

SAJOUS'S
ANALYTIC CYCLOPEDIA
OF
PRACTICAL MEDICINE

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Preface

EACH year there emanates from the laboratories, clinics and hospitals of this and other countries, an ever-increasing amount of important work, both experimental as well as clinical. There is scarcely a field in medicine, surgery, the various specialties and medical sciences that is not represented to a greater or less extent in this formidable array of contributions.

The year 1938 proved no exception. Indeed it is conspicuous because of the number of noteworthy advances that have been made during the past 12 months.

The Editors and Publishers of the *Cyclopedia of Medicine* have long realized that it is impossible for any individual to keep abreast of the ever-changing advances in medicine. Therefore, in order that the subscribers to the *Cyclopedia of Medicine* may have at hand in a readily available form a concise, critical survey of the progress that has been made in medicine, surgery and their allied branches, a Service Volume has again been prepared. This present volume is based upon the world's medical literature for 1938. It is larger, more comprehensive and much more profusely illustrated than any of the preceding Service Volumes. The effort of the editors is to present a well-balanced but selected review of the important contributions that have been made during the past year. Their desire is to supplement the basic contributions that are to be found in the *Cyclopedia of Medicine*, thus keeping them up-to-date. A work such as the Service Volume is only made possible by the coordinated efforts of a number of outstanding contributors, selected because of their recognized ability in their special fields. In the preparation of this volume, the work of the Editorial Board has been supplemented by additions to its ranks, as well as the acquisition of a number of well-known contributors.

The format of the present volume conforms to that of the *Cyclopedia of Medicine* which it so well supplements. The volume is divided into the main subdivisions of medicine, surgery, ophthalmology, otorhinolaryngology, pediatrics, physical therapy and general therapeutics. Under the subject of medicine are taken up the well-known special fields of medicine, such as allergy, cardiovascular diseases, gastroenterology, hematology, etc., as well as dermatology, dietotherapy, neurology, psychiatry and clinical pathology. Under surgery will be found subdivisions dealing extensively with anesthesia, endoscopy, abdominal surgery, gynecology and obstetrics, orthopedics, radiology, surgery of the sympathetic nervous system, thyroid surgery and urology.

Lack of space makes it impossible to discuss in detail the interesting features of all the various sections of this book. Suffice to point out, that in each section

In this work the subject of general therapeutics has not been slighted. Adequate presentation will be found of the newer drugs which have excited so much interest during recent months; for example, heparin, mandelic acid, nicotinic acid, thiocyanate, vitamins, and particularly the sulfanilamide derivatives, including sulfapyridine, which appear to be revolutionizing the management of certain diseases.

To Dr. Edward Leroy Bortz, the Assistant Editor, belongs full credit for the conception of this volume, selection of the contributors and its general supervision. To him the Editor once more extends sincere appreciation and thanks. To Mr. George B. Johnson and to Dr. Frederick C. Smith his thanks are also due for their tireless and efficient work in preparing the manuscripts and seeing the volume through the press, as well as to Miss Mary Frank for her valuable secretarial assistance. The publishers are to be congratulated upon the excellent appearance of this volume and the liberality with which they have illustrated it. Without the enthusiastic support and cooperation of the Associate Editors and Contributors, a volume such as this would have been impossible. Thanks to this support, the Editors have been able to bring to the attention of the medical profession a volume in which they feel a just sense of pride, and confidence that it will prove of exceptional interest and of definite, practical value.

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MEDICINE

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and
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ALLERGY

By HARRY BOND WILMER, M.D., and MERLE MIDDOUR MILLER, B.S., M.D.

CHRONIC ASTHMA

Treatment—*Epinephrine in Oil*, "*Slow Epinephrine*"—An attempt is made to treat all asthmatics prophylactically and symptomatically but, in prolonged intractable cases of asthma, therapy is often predominately the latter. Many of these patients take daily from 6 to 12 or more injections of epinephrine, 1:1000 aqueous solution, in doses varying from $1\frac{1}{2}$ to 15 minims (0.1 cc to 1 cc). A way has been devised to decrease the number of injections by producing a substance that is absorbed more slowly. The aqueous solution of epinephrine is absorbed very quickly and eliminated rapidly and often it is very fleeting in effect. A solution or suspension of epinephrine in oil is absorbed much more slowly and the effect is prolonged.

E. L. Keeney,¹ has reported the results of his observations in a preliminary report and later, the above author and J. A. Pierce and L. N. Gay reported more clinical findings.² Epinephrine in oil or "slow epinephrine" is a suspension

of powdered epinephrine in peanut oil. It is best administered intramuscularly in the deltoid or gluteal muscle, especially if repeated injections are to be given. Occasional doses can be given subcutaneously in the buttocks.

In patients with acute attacks of asthma, it is often well to give a preliminary dose of the aqueous solution of epinephrine hydrochloride and follow later with a dose of epinephrine in oil. The average adult dose of "slow epinephrine" is 15 minims (1 cc). If the attack is severe, 22 minims (1.5 cc) may be given. It has been our experience that, at times, the "slow epinephrine" acts almost as quickly as the aqueous solution and also that doses smaller than 15 minims (1 cc.) will sometimes be sufficient. The average dose for a child from 2 to 5 years is $7\frac{1}{2}$ minims (0.5 cc), from 5 to 12 years 12 minims (0.75 cc).

In those patients who have a prolonged siege of asthmatic paroxysms or who have nightly attacks, the "slow epinephrine" can be given in the evening

before retiring. Fifteen minims (1 cc) can be given at that time and, if this holds the patient during the night, he can be given 12 minims (0.75 cc) or less on subsequent evenings. If 15 minims (1 cc) does not give the desired results, then 22 minims (1.5 cc) can be given. The dose may be gradually increased or decreased according to the individual and the severity of his paroxysms. Of course, "slow epinephrine" can also be given at any time during the day for the attack. A 1½ or 2 cc dry sterilized syringe can be used with a 22 or 23 gauge needle.

This preparation may also be used in cases of angioneurotic edema and urticaria. It is indicated in those cases that are refractory to all methods of elimination and hypersensitization. Here again the dosage is from 7½ to 22 minims (0.5 cc to 1.5 cc) depending on the patient's tolerance and the severity of his symptoms.

J. A. Murphy and C. Jones³ treated a group of cases and report good results in some very severe refractory cases. Approximately the same dosage was used as above. "Slow epinephrine" can be given to ambulatory patients the same as the aqueous solution.

From our observations and from the above reports, we believe that "slow epinephrine" is of value in the treatment of chronic refractory cases in that it decreases the number of injections as it has a more prolonged effect. At times, relief has been almost as prompt with the suspension in oil as with the aqueous solution. Therefore, it is not always necessary to give the latter as a preliminary dose.

Better results are being obtained lately from the use of 1:100 solution of epinephrine by inhalation. The reason is that more efficient glass atomizers are manufactured which deliver a larger

amount of a finer spray to the bronchial mucosa. At times, it should be given at regular intervals, *i. e.*, every 2 or 3 hours for 24 to 48 hours, with the hope of possibly building up an "adrenalin reserve" and breaking the asthmatic cycle. It may be given more frequently if the occasion arises. The use of an inferior atomizer may produce unpleasant and annoying dryness of the throat and, at times, gastrointestinal upsets from contact of the strong solution with the various mucous membrane surfaces.

J. B. Graeser and A. H. Rowe⁴ have obtained beneficial results in the treatment of bronchial asthma by the inhalation of a solution of epinephrine 1:100. For the spray, an atomizer should be used which vaporizes the solution to a degree sufficiently fine so that the particles will be disseminated to all parts of the lungs. The dosage varies with the patient and at the beginning it is a "trial and error" method. Caution must be observed but the only untoward symptoms noted have been severe headaches from prolonged use and a dryness of the throat. Only rarely have we noted any constitutional reactions. It is well to allow several minutes to elapse between deep inhalations. In a great many instances the use of the 1:100 solution by inhalation has supplanted the hypodermic injections of the 1:1000 solution. As a prophylactic, it is suggested that repeated inhalations during the free period of the day may prevent recurrent attacks or mitigate the severity of any paroxysm that might develop.

The aqueous solution of epinephrine is still the "drug of choice" in acute asthma. The best and most efficient results are obtained if the dose is given early, before marked bronchial edema and profuse secretion of mucus take place.

Many patients do not tolerate epinephrine well and for this reason we believe it is best to begin with $1\frac{1}{2}$ to 3 minims (0.1 to 0.2 cc.) the first time the drug is given, as reactions are quite common. The symptoms are tremor, pallor, nervousness, palpitation and cardiac distress. Also in many instances, these small doses will produce the same effect as larger doses. After the patient's tolerance is determined, the doses given should be governed by the severity of the attack. Epinephrine is not habit forming and may be used over a long period with safety.

There is no substitute for epinephrine in constitutional reactions following the injection of pollen extracts or sera. This preparation should be kept close at hand when any solutions, that at times produce anaphylactoid reactions, are given.

Often severe, intractable, chronic asthmatics build up a tolerance to adrenalin. The dose is gradually increased and still no effect is obtained. At this time, other measures must be taken.

I. S. Kahn⁷ presents 16 cases, all desperately ill, and in all of whom hypodermic injections of epinephrine in the usual doses were of absolutely no effect in relieving the asthmatic paroxysm. He believes that, when this drug in doses of the usual size has failed, its further indication and efficiency can better and more safely be determined, not by increasing the dose given hypodermically, but by proceeding cautiously intravenously. He suggests the use of a 1:1000 dilution in doses of 2 to 4 minims (0.15 to 0.25 cc.) using a tuberculin syringe and a 26 gauge needle. He states that, even if given in such small doses and slowly, this is an extremely shocking measure; terrific pallor, tremor, sweating, headaches, heart pounding and, at times, terrific nausea and vomiting occur almost instantly. He has never seen a

patient who has failed to develop either some or all of these symptoms. It is felt that some of these untoward reactions can be avoided or reduced by using a 1:10,000 solution. We feel that the administration of epinephrine by the intravenous method should be used only in extreme cases, very cautiously and in minute doses.

Certain drugs are valuable adjuncts in the treatment of mild or severe, acute and chronic bronchial asthma and deserve more detail.

Ephedrine may be given by mouth, but it is efficacious in mild cases only. The usual dose is $\frac{3}{8}$ to $\frac{3}{4}$ grain (0.0243 to 0.0486 Gm.) Often untoward nervous symptoms develop from the prolonged use of ephedrine salts. Synthetic ephedrine preparations, **propadrine**, etc., are of some benefit in mild cases and these usually do not give the unpleasant side effects we often get from ephedrine. J. H. Murphy⁸ reports that he has treated a group of patients with propadrine and believes the dosage of this preparation about equivalent with that of the ephedrine. He also feels that this preparation can be used over a longer period of time without any significant reactions. We believe that propadrine produces results in some cases but in our short series we have found that it is necessary to give larger doses than those usually found effectual when using ephedrine.

Morphine should not be given in acute asthma unless epinephrine has failed and, when given, morphine should be tried very cautiously, at first used in small doses. Many asthmatics have an idiosyncrasy to this and other opiates. Often morphine gives the rest needed by an asthmatic and it may have to be used. **Pantopon** and **dilaudid** can be used instead of morphine and good results

have been obtained with these two derivatives.

Atropine gives bronchial relaxation and dilatation but at times has an unpleasant drying effect on the secretions and renders the tenacious mucus in an asthmatic chest even more mucilaginous. It is often well to use it with the first dose of morphine. Subsequent or alternate doses of the opiate can be given without the atropine.

Bray,⁷ Black⁸ and others have used **glucose** intravenously in acute attacks in doses of $\frac{2}{3}$ to $1\frac{1}{3}$ ounces (20 to 50 cc.) of a 50 per cent solution. It may be given every 4 to 6 hours and then once or twice daily until the patient is well able to take sufficient carbohydrate by mouth. In these cases, the carbohydrate metabolism perhaps is normal but these patients, being cachectic and undernourished, are in need of this form of concentrated nourishment. If the patient is dehydrated, a 5 to 10 per cent solution in larger doses may be given slowly over a longer period of time if indicated. Some workers have been using a 50 per cent **sucrose** solution in doses of $1\frac{1}{4}$ ounces (50 cc.). This probably has a more prolonged effect and is possibly more dehydrating and seems to give better results. L. N. Gay recommends this form of carbohydrate intravenously and has treated many cases with this preparation.

The **barbiturates** and **bromides** often go a long way in allaying the fear of subsequent attacks and, in many cases, a nervous upset is the "trigger mechanism" that sets off an asthmatic paroxysm. Insomnia, nervousness and palpitation are often untoward symptoms following the administration of such bronchodilators and vasoconstrictors as epinephrine and ephedrine. The above drugs often go a long way in aborting attacks by doing away with the neurogenic precipitating factor. The neuro-

genic element is one of great importance in many manifestations of allergy.

Acetylsalicylic acid (aspirin) in the usual dose and combined with other drugs may and often does give relief. The exact mechanism of action is not explained but its promiscuous use in allergy is very dangerous as we have observed many allergic individuals who have a marked idiosyncrasy to this drug. Several times, severe constitutional reactions have been encountered. It is always well to inquire if the patient has previously taken aspirin with no ill effects. Any of the coal tar series may give untoward symptoms.

Calcium, orally or intravenously, has been used in many or all allergic diseases. This drug is very readily absorbed and tolerated in the gastrointestinal tract, so usually there is no need to administer it by any other route. It is very much of a question whether any allergic symptoms have been markedly relieved by calcium. The usual preparations are calcium lactate and gluconate 10 to 15 grains (0.6 to 1 Gm.) 3 to 4 times a day.

Waldrott⁹ first reported the use of **aminophyllin** (theophylline with ethylenediamine) in emergency treatment in asthma. He found this drug was particularly efficacious in the so-called "adrenalin-fast" cases. We have used aminophyllin by mouth in a great many patients with bronchial asthma who are not in status asthmaticus. It seems to be beneficial especially in those who have some myocardial damage and poor coronary circulation.

G. T. Brown¹⁰ believes that aminophyllin intravenously has proven of definite benefit in cases of status asthmaticus and may at times be a lifesaving measure. He recommends a dosage of 7.5 grains (0.5 Gm.) of aminophyllin in $4\frac{1}{2}$ to 5

drams (18 to 20 cc) of 50 per cent glucose and he injects the mixture slowly.

Theophylline orally is also of value in the treatment of mild or moderate cases of bronchial asthma. The dosage usually given is 2 grains (0.13 Gm.) of theophylline with the usual dose of ephedrine and phenobarbital or alone.

Iodized oil can be administered in several different ways, *i e.*, (a) the intranasal catheter, (b) gravity method, which is accomplished by pulling the tongue forward and allowing the oil to run down, (c) intratracheal instillation by a laryngeal syringe, (this technic is described by R. M. Balyeat, L. E. Seyler and H. A. Shoemaker¹¹), and (d) bronchoscopic application which some workers contend is by far the best method. For practical and routine use, it is felt that instillation by the laryngeal syringe is the most desirable means of administration.

Untoward reactions observed from the use of iodized oil are as follows: (a) Iodine sensitivity and iodism. Balyeat reports as a possibility. We have had 1 case in which quite marked edema and inflammation of the respiratory mucosa followed the instillation of the oil. Subsequently this patient was proven highly sensitive to iodine preparations. W. Anderson¹² observed severe iodism in 8 cases. (b) Convulsive cough often follows the introduction and there is a possibility of massive collapse of the lung or a lobular atelectasis. (c) Criepp¹³ encountered the following distressing symptoms: Severe dyspnea, cyanosis and circulatory failure from which the patients recovered. Plehn reported 1 case of traumatic bronchiectasis following a prolonged convulsive cough. (d) Pneumonia developed in 8 of Anderson's cases and all but 1 recovered. Other workers report oil in the lungs for months to years after the instillation. (e) Allergic reac-

tions characterized by urticaria, asthma, arthritis and fever have been referred to by different observers. A sensitivity to the oil used as a vehicle for the iodine is thought to be a factor in some cases.

Fatal termination to complications resulting from the use of the instillation of iodized oil is not rare and Criepp feels that all the disadvantages and possible untoward reactions noted above should be carefully weighed before treatment of this type is instituted.

Potassium, sodium and strontium iodide in doses of 5 to 15 grains (0.3 to 1 Gm.) 3 times daily is probably the best alternative and liberator of bronchial secretion available at present. Some allergic individuals cannot tolerate therapeutic doses, but this preparation is worth a trial in all asthmatics, especially of the intrinsic or mixed type.

Endocrine Therapy in Allergic Diseases

Many patients with allergic disease have associated with it some glandular dysfunction. We believe that a great many have some hypofunction of the adrenals, at least from their clinical symptoms. Truly allergic individuals are often asthenic, fatigue easily, have a soft compressible pulse and a low blood pressure.

These patients often do well on **adrenal extracts** both by mouth and parenterally. H. B. Wilmer and M. M. Miller¹⁴ have reported 13 per cent beneficial results in this type with intramuscular injections of **cortical hormone** processed by the Swingle-Pfaffner method. L. E. Prickman and G. A. Koelesche¹⁵ treated a group of 19 patients with suprarenal cortical extract (cortin). Six of this group showed some slight symptomatic relief. These 6 had asthma. One patient had complete relief of his symptoms from treatments given

2 months apart. In all the rest, no relief was noted. These observers conclude that the intravenous administration of cortical hormone, suprarenal cortical extract (cortin) and supplemented by sodium chloride by mouth gives little or no benefit in a group of patients who had asthma and other allergic diseases.

Suprarenal extracts by mouth have also been used with varying success. We have treated a large group of cases with **suprarenal concentrate** and **glycortal**. The dosage of each is 4 to 8 capsules daily. These can be given with or without the addition of **sodium chloride**.

These adrenal extracts, whether given by mouth or injection, do not have any marked specific effect in the symptomatology of allergic disease but they are adjuncts in treatment. They are to be used as supplementary therapy to the usual elimination and hyposensitization.

It is believed that they help reinforce the primary background of endocrine and nervous stability that is so often lacking in the allergic individual. At present, if an allergic patient manifests the clinical symptoms of hypoadrenia, it is well to supplement the usual therapeutic measures with a whole gland adrenal preparation.

Endocrine therapy is often of extreme importance, especially in patients at the *menopause*. Preparations containing female sex hormones are often indicated in cases with complications associated with menses and the menopause. We have used **progynon B** and other estrogenic substances in doses varying from 500 to 2000 rat units at intervals of 4 to 5 days, beginning about a week after the last period and continuing until the next. After cessation of menstruation, the dose is given at the same interval, and the amount depends on continued indication or untoward symptoms developing.

Thyroid extract has proven a valuable adjunct in cases where there is clinical evidence of hypothyroidism or a low basal metabolic rate, or both. A combination of thyroid extract and suprarenal concentrate has been highly efficacious in some of our cases.

This fundamental condition from which allergy inevitably results must be found before there is any marked advance in therapy. In the opposing action or synergistic functional activity of any 1 or group of glands may be found the answer.

Potassium Salts in Allergy

H. A. Rusk and B. D. Kenamore¹⁶ treated a small series of cases of urticaria with a **high protein, low sodium, acid-ash diet**. They added to this **potassium chloride** in doses of from 60 to 90 grains (4 to 6 Gm.) daily. They felt that there was a sound physiologic and therapeutic basis in that these individuals suffering from urticaria and an angioneurotic edema had an altered mineral balance. It was through the work of Nathan and Stern that there was found a low serum potassium level in certain dermatoses. Klauder and Brown¹⁷ reported a direct relationship between the serum potassium and skin irritability. Other observers have shown that pharmacologically potassium at times produces a reaction almost analagous to that of epinephrine.

This group of patients was observed clinically only and no laboratory determinations of significance were done. The diet given was made up largely of proteins, vegetables and noncitrous fruits. No salt was served with meals but potassium chloride was used instead of sodium chloride. The caloric value of the diet was arranged to suit the patient. In brief, the diet is as follows:

Fruits—noncitrous, fresh or stewed.
 Vegetables—especially beets, carrots, Brussels sprouts, corn, lettuce, mushrooms, peas
 Meat and eggs twice daily
 Milk—1 glass and $\frac{1}{2}$ glass of cream
 Salt-free butter
 Bread, cereal and starches—a limited amount.

Following the therapeutic approach of the above workers, R. E. Cohen¹⁸ reported a small group of cases in which he used a high protein, low sodium, acid-ash diet. Rusk and Kenamore treated 6 patients.

In 8 cases treated in the same manner, no improvement was noted during or following the régime and the benefit derived from this therapeutic approach seems doubtful.

B. Bloom¹⁹ reported striking results from the use of potassium chloride in *hay fever*. He gave much smaller doses than previously reported. Instead of 15 grams (1 Gm) every 4 hours in enteric coated capsules, 5 grams (0.3 Gm) in a full glass of water was given. This procedure in most cases eliminated the untoward gastrointestinal symptoms first noted. This dose was given only 3 times daily.

If, as recent work has shown, in endocrine dysfunction there is a disturbance of electrolyte balance and if allergy is based on an endocrine imbalance, then this might be a rational approach. The authors of this section feel that clinically we can demonstrate glandular hypofunction in a great many allergic individuals but we have never been able to demonstrate any disturbance of electrolyte metabolism in allergy, following a great deal of work. An exhaustive laboratory study from the standpoint of salt and water balance in these individuals has been done.

In the above report, striking benefit was noted in 29 cases of *hay fever* after the use of potassium chloride. This

preparation was tried in other allergic diseases and it was found practically ineffectual in chronic asthma, but, when used along with a low salt diet, it seemed helpful. No toxic untoward effects were noted from the use of potassium salts.

We have used potassium chloride in about 30 allergic cases and have not had any markedly significant results. Gastric distress was noted in a large percentage of our cases but this was decreased by giving a weak solution as recommended by Bloom. Most of our patients using potassium chloride had urticaria and in no case did we have a marked clinical improvement. We must always remember in treating allergic diseases, especially urticaria, that there are frequent remissions and exacerbations.

Irradiation in Treatment

C. K. Maytum and E. T. Laddy²⁰ in 1936 reported their results on the treatment of refractory bronchial asthmatics by the use of *x-rays*. Their report at that time included 23 cases. These same authors²¹ report this year the results obtained in treating 161 patients with moderate and severe bronchial asthma. Twenty-four per cent obtained marked relief. Moderate relief was noted in 16 per cent and 14 per cent obtained marked relief, but other treatment given at the time may have been the more important procedure. Forty-six per cent of these patients had less than 50 per cent relief and were classed as failures.

Roentgen therapy does not replace the usual treatment given an asthmatic but at times it is a valuable adjunct in the treatment of intractable cases. Also the warning is given that it should not be used indiscriminately as considerable harm may follow overdosage or too frequent use. The beneficial results from x-ray treatment are often only temporary and not a curative measure. The formula

given by the authors is as follows: kv. 135; filter 6 mm Al; distance 40 cm, ma. 5; time 25 minutes = 500 R

Irradiation at first was given over the mediastinum through 2 paravertebral fields. Later they have been using the anterior and posterior fields in the mediastinum but it is possible that the latter method is harder on the patient and probably produces no better results. Epinephrine is often given just before or during the treatment.

We take the liberty of quoting Dr Maytum in his opinion of x-ray treatment: "Any qualified roentgenologist, however, should know the dosage that the skin will tolerate and the interval at which it can be repeated. Also, treatment should be given only by such a qualified roentgenologist. The recommended dosage should not do harm if the intervals are a month or more apart and if treatment is not repeated too frequently."

Rest in Treatment

A hospital is the ideal place for complete relaxation and rest. It has been the writer's experience in many cases that hospitalization *per se* was enough to give a patient complete relief, without any medication, hyposensitization, etc. Improvement practically always follows continued rest, both physical and mental. Complete rest is the first and most important part of any acute asthmatic regimen.

Piness once made the statement that if the individual in status asthmaticus is given complete physical and mental rest, plus fluids, he will usually come out of the attack in good condition. As we have previously stated, there are many adjuncts in the treatment of bronchial asthma but, first and most important, is complete rest.

B. A. Credille²² stresses the importance of rest in the treatment of allergic diseases. Fatigue and exhaustion are very vital secondary factors and, as has been found, often the most important mechanism in precipitating an attack. He believes that an allergic individual has a definite fatigue threshold. When this is lowered, the patient is more likely to have an attack. Prolonged rest is a most valuable adjunct in the treatment of asthma, asthmatic bronchitis and the like. This is especially true of the "high strung," nervous type of patient.

Differential Diagnosis of Asthma

In the diagnosis and treatment of chronic asthma, particularly intractable and refractory cases, we are constantly confronted with, first, the problem of differentiating between bronchial asthma and a paroxysmal dyspnea of cardiac origin, secondly, we always think of possible untoward effects of the repeated use of bronchodilators which are usually vasoconstrictors also, particularly epinephrine.

Age is very definitely a factor and in those patients over 50, whether they have had asthma for a long period or for just a short time, clinical cardiac involvement is frequently found.

We have had the opportunity of observing at postmortem 4 cases in which death was due to bronchial asthma. Two of these have been reported²³. Three of the 4 were under 40, 1 only 26. In none was there any clinical evidence of cardiac damage even with rapid pulse, pallor, irregular rhythm and heart consciousness. Nor was there any pathologic, macroscopic or microscopic evidence of damage. In 1 case which came to autopsy, the coronary vessels were injected with mercury and x-rayed. All of these patients had received epinephrine paren-

terally over a long period and in doses varying from 0.2 cc. to 1 cc.

The problem of differential diagnosis is very perplexing at times F. M. Smith and W. D. Paul²⁴ feel that this pertains particularly to cases in which there is a long history of asthma with marked emphysema or in those who have reached the age where degenerative lesions occur in the heart. As we have found, they also find this problem more often in cases in which the onset of dyspnea, cough and wheezing is late in life and in which there is evidence of both pulmonary and cardiac disease. These authors also cite a case in which they believe that clinically epinephrine had a deleterious effect on the patient's cardiovascular system

W. A. Colton and T. Ziskin²⁵ call attention to the summary of Michael and Rowe, which we believe is one of the most comprehensive in a subject of which little is known and on which only a small number of cases has been published from the pathological standpoint. The consensus is that all cases of bronchial asthma that are autopsied should be reported. We have been inclined to agree with Coca²⁶ that the heart is very probably injured very slightly, if at all, in bronchial asthma but Kountz, Alexander and Prinzmetal,²⁷ after careful investigation, have found that there is evidence of right ventricular strain in bronchial asthma. Colton and Ziskin conclude as follows: "that the heart does not remain singularly free from injury in bronchial asthma, and that right ventricular strain with a tendency to myocardial involvement and heart muscle damage does occur as the disease progresses and emphysema ensues."

From the above investigation and also from experience with asthmatics with cardiovascular involvement, we feel that the heart should be carefully studied in

all cases of asthma. Also during treatment, myocardial involvement should be looked for, especially if the patient is taking frequent injections of epinephrine. This drug is fleeting in effect but must be handled with care and, as has been previously stated, should be used in as small doses as possible

HAY FEVER

Treatment—At the present time there is only 1 recognized method of treating seasonal hay fever. This is *specific hyposensitization* to the pollens to which the patient is sensitive. This sensitivity has previously been determined by tests, either scratch or intracutaneous. We recommend always doing the scratch test first and, if no significant reaction is elicited, then the intracutaneous tests should be done. There are different ways of standardizing pollen extracts and also various dosage schedules but we should like to present the 3 methods of hyposensitization and attempt to choose the most efficacious.

The 3 methods of treatment are the preseasonal, coseasonal and perennial. We can discuss the coseasonal procedure in a brief space. We commence pollen hyposensitization during the season only because the patient has failed to prevent himself for treatment before the onset of pollination. There are more chances of failure and the patient is more liable to a generalized reaction if treated entirely while he is absorbing pollen from the air. This disadvantage is eliminated to some degree by a routine we have followed in the past 2 years both in pollen asthmatics and in hay fever cases. Rapid hyposensitization is attempted and especially works well if the patient is placed in an air-conditioned pollen-free room.

In reviewing the literature from 1920 to the present, one finds that Besredka

was the first to desensitize an individual *via* the rapid inoculation method. The title of his paper was "De Lavaccinatin Anti Anaphylactique" published in *Compt Soc de Biol.* 1908, 65, 479.

In 1930 John Freeman published an article "Rush Inoculations" in the *Lancet*. His paper deals with the rapid hyposensitization with pollens in the treatment of hay fever and pollen asthma. The injections were given every 2 hours, starting with 80 units and reaching 20,000 within a period of 3 days. Of course, not all patients receive such high dosages. He believes that this method has its definite advantages in that it is not time consuming and that reactions can be prevented by careful nursing observations during the 3-day hospital period.

In 1937 Waldbott and Asher²⁸ published a paper entitled "Further Observations on Rapid Hyposensitization." This was a follow-up of an article published in the *Journal of Allergy* in 1934 by the same writers. Their conclusions were:

1. One is able to reach a high state of hyposensitization.

2. There is certainly some danger attached to this method.

3. Late reactions occur more commonly.

4. The danger of reaction was lessened by the administration of several minute doses at the onset of the treatment.

Nineteen cases of pollen asthma were treated in this manner. A complete course of pollen injections was given at intervals of 1 to 2 hours. The first dilution given was 1:10,000, and the first dose was 1½ minims (0.1 cc.). The maximum dose given was 7½ minims (0.5 cc.) of a 1:500 dilution. Sixteen of the 19 cases were completely hyposensitized and remained so during the rest of the season. Some have been put on perennial treatment while others we have allowed

to go until the next season. One case became very toxic during the period of treatment and this procedure had to be discontinued. Two of the patients had no relief whatever. There were no more constitutional reactions encountered than we usually get in the preseasonal treatment. In only 1 case was it necessary to stop the injections.

The coseasonal procedure was attempted in 21 cases of hay fever during the last season, 8 were spring grass cases and 13 were sensitive to different fall weeds. Good results were obtained in 2 of the spring cases and 6 had complete relief. Two cases were treated in air-conditioned rooms. The spring season of 1938 was not a very bad one but at times symptoms were quite marked.

Our results with the 13 fall cases were not as striking. The fall season in the Middle Atlantic States was one of the worst in several years. Four patients had complete relief, 7 had some relief, at least 50 per cent, and 2 patients had no relief. Unfortunately, only 2 of these patients were treated in air-conditioned, pollen-free rooms.

Precautions observed were:

1. If any local reaction was observed, the same dose was repeated or the interval lengthened to 2 hours.

2. The patient was entirely removed from contact with the offending substance.

3. Four of the patients were put in air-conditioned, allergen-free rooms.

4. Patients were hospitalized and kept in bed under constant supervision during the period of hyposensitization.

5. Injections should be stopped if any constitutional reactions develop.

A Vander Veer²⁹ reports a study of the relative merits of the seasonal and perennial treatment of hay fever. At present, there is a great deal of contro-

versy among allergists as to the better method. This article dealt with observations on an average of 430 patients annually. A questionnaire was sent to each patient who alone evaluated the results obtained. According to the chart published in the résumé, it was shown that the perennial results were uniformly better by 8 to 10 per cent than the seasonal. This is according to statistics, but the human equation must be brought into the picture. It is much easier to persuade a patient with complete relief to continue throughout the year than 1 who has been refractory to the seasonal injections. This factor may tend to place more of the satisfactory cases in the perennial group.

There are 2 disadvantages in the perennial treatment. Many patients forget to take the injections and, if an interval of 5 weeks has elapsed, the risk of constitutional reaction is increased. There is always the possibility of a patient becoming saturated and into such a state that very small injections will give a constitutional reaction.

In general, the problem is best solved by choosing the right method for each patient, depending on temperament, sensitivity and previous results obtained. The preseasonal and coseasonal methods of treatment are quite necessary in many cases but, under ideal conditions and when there are no untoward symptoms, it is felt by a great many allergists that the perennial treatment is, by and large, the method of choice. Vander Veer considers that perennial treatment is more likely to produce a permanent so-called "cure" eventually than the other methods.

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ARTHRITIS AND RHEUMATOID CONDITIONS

By RALPH PEMBERTON, M.D., and C. W. SCULL, M.D.

ARTHRITIS

Incidence—The extent of the public health problem constituted by chronic rheumatoid diseases is not widely appreciated. Part of the reason for this has been the lack of comprehensive data bearing upon this problem in the U. S. A. Surveys already reviewed have indicated the wide extent of these diseases in European countries and in the States of Massachusetts and Maryland. The United States Public Health Service has published data¹ based upon a house to house canvass of 800,000 families, including 2,800,000 persons living in 19 States. The results obtained have provided with appropriate statistical methods an estimate of the extent of the chronic disease problem throughout the country in terms of the number of persons afflicted with certain groups of diseases. In addition economic cost in terms of days lost and the number of persons disabled by these diseases has been estimated. The incidence of rheumatism so calculated is estimated at 6,850,000 persons. The term rheumatism includes arthritis, gout, neuralgia, neuritis, lumbago, etc. This number exceeds that of any other single group of chronic disease and is followed by heart disease with 3,700,000, arteriosclerosis with 3,700,000, hay fever and asthma with 3,450,000, hernia with 2,100,000, hemorrhoids with 2,000,000, varicose veins with 1,750,000. Further interpretation of these data may be obtained by comparison with the fact that approximately 6,000,000 persons are afflicted with syphilis. The importance of the latter as a public health problem is widely recognized.

Additional appreciation of the importance of this group of diseases is to

be seen in the disability as measured in terms of the days lost from work because of rheumatism. The number of days annually lost from productive work due to rheumatism is placed at 97,200,000, which is exceeded only by the loss from nervous and mental diseases, which account for 132,500,000 days, and nearly equalled only by heart disease, which accounts for 95,200,000 days. These groups are followed in the order of decreasing total number of days lost from arteriosclerosis, tuberculosis, cancer and nephritis. The relative economic waste occasioned by rheumatic diseases as compared with other chronic diseases is made graphically evident by these figures.

The relation of economic status to the days of disability per person per year occasioned by rheumatism is indicated in the report of the United States Public Health Service.² The disability per person per year from rheumatism of all income groups is 0.78 days for the age group 25 to 64 years and 4.12 days for the age group of 65 years and over. Only 6 per cent of the disability from rheumatism occurred among persons under 25 years of age. The relief group showed 1.80 days disability for ages 25 to 64 years while the relief group showed 7.44 days for the age group 65 years and over. The nonrelief group with an annual family income under \$1000 showed 1.00 and 4.45 days disability in the younger and older groups respectively. Groups with incomes from \$1000 to \$1500 showed 0.59 and 3.39 days for the younger and older groups. Groups with family incomes above \$1500 per year showed only 0.45 to 0.41 days and 3.08 to 2.37 days of disability per person per year in the younger and older age

groups. Over 50 per cent of the days of disability due to rheumatism occurred in the groups on relief and in families on incomes under \$1000 per year. Over 50 per cent of the cases occurred in the same low income groups. These data demonstrate the fact that poor living conditions increase the risks of development of rheumatism and suggest the doubtful economy of limiting to an extremely low income a portion of the nation's population.

Further evidence regarding the extent of the human waste occasioned by these conditions is shown by the number of persons who were made invalid for a period of 12 months prior to the day of the survey. There were 147,600 persons so handicapped. This group was exceeded only by the number of persons disabled with nervous and mental diseases, *viz*, 269,300. Rheumatism was followed in order of decreasing numbers by heart disease, tuberculosis, arteriosclerosis and high blood pressure, diabetes mellitus, nephritis, asthma, cancer and other tumors.

Proper and deserved public attention has been directed toward the care and study of some of the numerically smaller groups. In contrast, a minimal amount of public support has been directed to the study and care of rheumatism. It appears that the problem of rheumatism should have an increasing degree of attention as interest is aroused in the problem of chronic disease. Chronic disease though less dramatic than acute diseases exacts a high human toll and should be combated with equal vigor.

Diagnosis—Pathological — Additions to the knowledge of pathology of arthritis are infrequently made, because of the paucity of material obtainable during the active phases of the disease. The contribution by Ghormley, R. K. on the pathology of nonspecific arthritis³

presents observations on material obtained from various forms of surgical procedures. The author considers that in atrophic arthritis the most important pathological changes occur in the synovial membrane. These pathological features are marked by hypertrophy or proliferation of the membrane which shows irregular thickening and encroachment upon, and firm attachment to, the cartilage. The most prominent histological features include: (a) A surface or multilayer of flattened cells sometimes swollen, (b) a vascular network extending up into the villi, (c) an interstitial network of loose areola showing edema, and finally (d) collections of small round monocyctic cells, more or less abundantly scattered throughout the membrane. The latter collections constitute a feature superficially similar to tubercles in structure. The collections are not perivascular but rather are built up in a special stroma. The central portions are filled with epithelial-like structures surrounded with tightly packed lymphocytes. Occasionally mitotic figures are seen. The relative importance of these collections is emphasized by the fact that of 59 synovial membranes, 40 showed such collections in all sections and 17 showed collections in some sections; and further by the fact that such lesions were found in all but 5 cases clinically diagnosed as proliferative arthritis. The presence at various stages of development within a single membrane suggests that the appearance of focal collections is associated with periods of exacerbation of the disease. The stimulus producing the sequence of changes is, according to Ghormley, "probably chemical rather than bacterial." The growth of the proliferating pannus "chokes" the cartilage. Fibrosis is the essential feature marking the arrest of the active process. Bone changes also occur, with regions of in-

filtration of fibroblasts from the marrow spaces beneath the subchondral plate. Focal collections similar to those in the synovial membrane may be found in these areas. The joint capsule may also exhibit extensive fibrosis probably arising from the adjacent synovial membrane.

The characteristic features of hypertrophic arthritis are found in the cartilage, the earliest change consisting of fibrillation extending through the cartilage from the surface to the subchondral plate. Irregularity of arrangement of the cartilage cells develops, finally leading to a thinning of the cartilage in the central area. Apparently a compensatory process starts, resulting eventually in a thickening of the subchondral plate. At the periphery the process of wear is not so complete so that areas of fairly thick atypical cartilage with islands of osteoid tissue develop. The net result of these peripheral changes is the production of osteophytes or spurs. At the same time the synovial tissue becomes somewhat thickened with an increase in number and size of the villi. Both fibroblasts and fatty infiltration are seen, but the focal collections of round cells are conspicuous by their absence. In addition to the changes in the region of the subchondral plates, the bone may show cystic degeneration. The cysts are usually filled with amorphous tissue without characteristic cytology. Ghormley is impressed with the similarity of the pathological processes in hypertrophic arthritis to those of traumatic arthritis. The common sequence of pathological changes is attributed to the relatively avascular structure in cartilage. The nutritive supply to cartilage provides only a small margin of safety so that injury to a central area is not readily repaired and there ensues a progressive train of events leading to the end results cited above. On the basis

of the pathological differences Ghormley considers that his observations confirm the view that there are 2 types of non-specific arthritis which are characterized by distinctive pathological pictures.

X-Ray Diagnosis—The radiological features presented by joints are important but have unappreciated limitations according to G. VanDam.⁴ The roentgenogram of the joint presents a macroscopic picture of bone, a negative representative of the cartilage, by absence of shadow, and, when made with special technic, some indication of the condition of the soft parts. Usually no evidence of alteration of the synovial membrane is revealed and generally no reflection of important early changes of bone, *e g.*, hyperemia and early cartilage changes. Even such defects as cavities in the cartilage of the knee must reach considerable size before being made evident by the roentgenogram. According to the author clinical signs, *i e.*, those giving direct evidence regarding the joints, muscles and skin are of quite as much significance as are the features revealed by x-rays. Data revealed by x-rays cannot be expected to be used alone as a basis for evaluating the pathological condition of the joint.

Despite these limitations several important diagnostic criteria may be obtained by a study of roentgenograms. Heberden's nodes are described as a composite structure made of a large periosteal osteophyte connected with the periosteal head of the phalanx and a pointed cartilagenous osteophyte connected with the cartilaginous base of the next phalanx. The carpometacarpal joint of the thumb may be similarly attacked fairly frequently in hypertrophic arthritis. The usual sites of involvement are the proximal and distal interphalangeal and the basal joint of the thumb. In the phalanges the first sign of hypertrophic arthritis is seen in the unilateral disap-

pearance of cartilage in the distal interphalangeal joints.

In atrophic arthritis an early sign in the hand is a transverse contracture of the palm which can be recognized in the roentgenogram by a comparative shift of the ulnar projections toward each other. Erosion of the heads of the metacarpals on the radial side is likewise often seen.

The pathological changes in the different joints are variable. In the shoulder marked degree of clinical disability in terms of limited motion, and crepitus may be present, but the radiological survey often fails to reveal marked changes in the bone and cartilage of this structure. However, this may be accounted for by the fact that this joint is chiefly a muscular and ligamentous one.

For the diagnosis of changes in the cartilage, menisci and cruciate ligaments the injection of the joint with an opaque fluid or air is recommended.

The earliest roentgenologic change evident in atrophic arthritis in the spine is a sclerosis in the sacroiliac joint. This early localization is attributed to the fact that this joint is slightly mobile, rather than to the existence of a focus of infection at this site. In addition to the familiar lesions, *viz.*, calcification of ligaments, attention is directed to periosteal growth in the ischium and pubis frequently seen. In contrast to the ankylosis of the sacroiliac in atrophic spondylitis the absence of this feature is noted in hypertrophic spondylitis.

Physicochemical Diagnosis—The application of procedures to the fluid tissues of arthritics which reveal properties distinguishing such fluids from normals is always regarded as a step toward a fuller understanding of the nature of the disease. When such data appear to parallel certain clinical features the suggestion is advanced that such tests

may be utilized as objective criteria of the efficacy of treatment. Upon such grounds the *formol-gel test* is recommended by H. J. Gibson and E. W. Richardson⁵ as an additional clinicopathological criterion of activity in chronic rheumatism. In order to evaluate the test observations with standard methods were made upon the sedimentation rates of the bloods studied. After the sedimentation rates were determined the formol-gel tests were made according to the following procedure. The venous blood (15 cc.) oxalated with 0.3 ml of 10 per cent neutral potassium oxalate is centrifuged at 3000 r.p.m. for 15 minutes. One milliliter of the clear plasma is transferred to a test tube (Wassermann) followed by 1 drop (0.04 ml.) of formalin (36 per cent formaldehyde). The tube is shaken, and placed in a rack sufficiently inclined to permit the fluid to cover the side of the tube. At intervals of 15, 60 and 120 minutes and after 18 hours the tubes are tilted to the vertical position to estimate gelation. The time for the appearance of gelation is recorded. Temperature effects are negligible between 70° and 98.6° F. (21° and 37° C.).

Plasmas showing positive gelation within 2 hours are subjected to a quantitative test carried out as follows. A series of 6 tubes are prepared with 0.9, 0.8, 0.7, 0.6, 0.5, 0.4 ml. plasma and diluted to 1.0 ml. with normal saline. One drop of formalin is added, the tubes shaken and placed in a tilted rack. At the end of 18 hours the degree of gelation is estimated. The relative degree is designated as 1 plus, 2 plus, 3 plus complete coagulation undiluted plasma, 4 plus complete coagulation 0.9 to 1, 5 plus complete coagulation 0.8 to 1, and so on to the highest dilution.

A statistical analysis based upon a series of 100 cases with respect to the

degree of correlation of sedimentation rate and values for the formol-gel test reveals that there is a real association of the values. Furthermore, this association is independent of the procedure used for the sedimentation rate. There is also a certain degree of parallelism between high F. G. reactions and anemia among the rheumatics. However, anemia may be present without a high F. G. value, indicating that the active rheumatic process may increase the F. G. value and at the same time increase the degree of anemia. One group of rheumatisants shows a high sedimentation rate but a low value for F. G. reaction, *viz.*, gout. The reason for this discrepancy is not apparent to the authors.

The test is in most instances a less sensitive indication than the sedimentation rate but is regarded as a useful supplementary test. It is to be observed that positive reactions are present in kala-azar and in a certain proportion of cases of syphilis. Less marked but positive reactions are also present in leprosy, pulmonary tuberculosis, dysentery and gonorrhea. Positive reactions, though less marked, are present in the blood sera as well as in the plasma. This indicates that fibrinogen is not the only factor involved in producing a positive reaction. There is suggestive evidence that the level of the euglobulin fraction of the plasma and serum proteins is a significant factor in producing positive reactions. The simplicity of the technic and the high incidence of markedly positive reactions in the formol-gel test provide sound basis for more extensive utilization of this technically simple procedure.

Therapy—Allergy—The view that arthritic diseases are allergic in nature and origin provides the basis for several forms of therapy, *viz.*, **desensitizing doses of vaccines**, certain **dietetic measures**. The relevance of such pro-

cedures depends largely upon the question of the extent to which the pathological processes involved in the diseases are determined by allergic phenomena. A critical and illuminating discussion of the relationship is presented by Aschoff.⁶ Aschoff restricts the use of the concept of allergy to those conditions marked by a peculiar abnormality or excessive degree of sensitivity leading to paroxysmal manifestations. Since arthritis does not exhibit such features as primary characteristics the arthritides are at once separated from the true allergic diseases. The view has been advanced, however, that arthritis resembles tuberculosis in certain respects and the latter shows certain features of excessive sensitivity which are regarded as manifestations of allergy. However, it is pointed out that it is not the phenomena of acquired sensitivity to certain products but the tubercle bacillus itself which is responsible for the disease. The second attack of tuberculosis is different from the first attack and hence it is proper to consider that an allergic phase has developed in the course of a primarily infectious disease.

According to the view of Klinge, there is a pathological similarity of the rheumatic nodules to experimental lesions produced by serum injections. Both types of nodules are characterized by fibrinoid degenerations. This common feature leads to the hypothesis that the rheumatic nodules must likewise be due to a hyperergic mode of formation. Aschoff does not accept this explanation for 2 reasons. In the first place the rheumatic nodule does not seem to develop primarily upon the basis of fibrinoid degeneration and, in the second place, the clinical pattern of rheumatic fever is so different from the true arthritides that it does not appear logical to regard all cases identical in origin simply on

account of a secondarily developed pathological similarity. This view is supported by the fact that many different kinds of stimuli may produce fibrinoid swelling.

It is further pointed out that localization of disturbance in a joint is often attributed to sensitivity. The absurdity of regarding this proposition as an essential explanation is indicated by the fact that certain chemically simple compounds such as urates seem to have a tendency to localize in renal and vascular tissues. Furthermore, certain pigments exhibit a tendency to accumulate in parts of cartilage or bone. By the same token, localization of tuberculosis, syphilis, or gonorrhea in joints may be more reasonably determined by influences such as trauma and age rather than by allergic factors or sensitivity in the classical sense. Furthermore, treatment of the latter conditions is more effective if directed toward the primary infective causes than if aimed at the secondary allergic manifestations which may be associated with them. By the same token, therapeutic effort should be directed toward the primary cause of the arthritis.

The unrestricted use of vague concepts of allergy as a basis for therapy in arthritis is clearly unwarranted. The fact remains that the agent or agents responsible for rheumatic fever as well as the hypothetical agent which produces atrophic arthritis are unidentified. Therapeutic approach should, according to Aschoff, be restricted toward a frontal attack on the "primary" cause. The patient requires care for the effects of disease, as well as for the precipitating factors.

Endocrine Therapy—The possible contributory effect of endocrine deviations to the development of arthritis remains as a prominent consideration in the minds of a number of investigators

In the past, attention has been centered principally on therapeutic trial of various active agents which might correct some of the clinical features associated with the states of hyper- or hypofunction of the thyroid, pancreas and parathyroid. The fact that the B. M. R. is low in a number of cases of rheumatic diseases has suggested the use of thyroid substance. **Thyroid therapy** had a rather thorough study at the hands of a considerable number of students. It has become evident that thyroid is useful only in a limited number of patients, *viz*, those in whom the reduced rate of metabolism is not due to a physiological exhaustion. Guided by similar considerations the fact that some arthritics present delayed rates of glucose removal suggested that **insulin** may be desirable as a therapeutic agent. In the light of reported studies it appears that insulin is useful chiefly as a stimulant to appetite in patients who have a diminished desire for food. It may also be recalled that **parathyroid-ectomy** has been advocated as a means of correcting an allegedly abnormal calcium distribution, particularly in patients with calcification of the spinal ligaments. The lack of clear-cut evidence that the atrophic spondylitics have altered calcium metabolism of the kind present in patients with marked hyperparathyroid function has minimized the significance of this approach.

The superficial similarity of the joint enlargements and acromegalic symptoms of Heberden's nodes long ago led to the view that pituitary dysfunction may be responsible for some of the joint changes seen, especially in hypertrophic arthritis. The experimental observations of Silberberg showing that anterior pituitary extracts produce lesions of articular cartilage similar to those seen in hypertrophic arthritis, have added further relevance to these considerations. The fact

that hypertrophic arthritis generally develops at the time of life (*viz.*, middle age) when changes in the pituitary and its dependent tissues are marked lends credence to this view. These endocrine relationships have been so apparent that rheumatisants have been designated as climacteric arthritics. Clear-cut definition of such a symptoms complex has not yet been fully established. A paper by A. P. Cawadias⁷ reviews the rationale and presents a technic for the application of *oestrin* in the treatment of certain morbid conditions associated with the arthritic syndrome. Cawadias assumes that all rheumatic diseases, including hypertrophic arthritis and to a certain extent atrophic arthritis, are manifestations of constitutional metabolic disorders, and that the joint symptoms are to be regarded as secondary manifestations.

According to Cawadias, production of arthritic manifestations in women appears as a result of ovarian insufficiency. These deficiencies arise from, and are associated with, an elaboration of toxic products acting directly on the joints and adjacent tissues, and by hyperactivity of the growth hormone of the anterior pituitary, the latter being a resultant of the state of hypo-ovarianism. As representative of the former type the alcaptonuric is cited in whom homogentisic acid, a product of disturbed tissue metabolism accumulates in the joint with a resultant production of arthritic lesions. In support of the biological probability of the second mechanism, the fact is cited that abrupt cessation of gonadal function is followed by an hypersecretion of the growth hormone. The growth hormone has a distinct action on the joints.

Acromegaly is often evident in the big toes and hypertrichosis occurs in children affected by rheumatism. In the syndrome of acromegaly a special type

of hypertrophic exostosis appears. These data considered with the observations of Silberberg quoted above, lend support to the view that hypogonadism with its attendant hypersecretion of the pituitary may, in fact, provide a mechanism whereby joint lesions develop. However, it is recognized that such deficiency alone does not account for the arthritic syndrome since many cases of gonadectomy do not always develop rheumatism. To the reviewers this fortunate failure may be due to more adequate compensatory circumstances in these cases, *i. e.*, physiological adjustments may be made without the occasionally attendant hypersecretory activity which, if present, would lead to the development of joint lesions. However, Cawadias passes over the possibility without mention in order to assay the role of another, perhaps more significant possibility, *viz.*, the local destructive influences acting concomitantly upon the tissues. Cawadias refers this to a disturbance in sulfur metabolism of the patient who is subject to the development of rheumatism. The data on this point, *i. e.*, the specificity of the sulfur factor, are not sufficiently complete to constitute proof but it does appear probable that some components of joint tissues are for some undefined reason different from normal and hence possess physical properties less resistant to insults of various kinds, including trauma.

Cawadias states that surgical or radiological castration is almost constantly associated with chronic rheumatic symptoms classified, pathologically as fibrositis or osteoarthritis (hypertrophic) with localization in the limbs in the latter case. For such cases large doses of *oestrin* are advocated. Initial doses of 1 to 2 mg. per week (10,000 to 20,000 I. U.) of oestradiol benzoate is recommended. Reduction or increase of dosage is made according to general clinical

indications Attempts at precise laboratory control of dosage are regarded as superfluous at present. *Oestriol*, 0.06 mg capsules, 2 or 3 times per day by mouth, is administered as an alternate method Such therapy is regarded as a depressant to the anterior pituitary.

Other states of hypo-ovarian function arising from toxic or infective influences require lesser amounts of oestrin given intermittently. Doses of 0.1 mg of *oestradiol* are recommended. Additional therapy with the *gonadotropic factors* of the anterior pituitary is also indicated.

The symptoms of climacteric hypo-ovarianism are due in part to hyperactivity of the anterior pituitary associated with phases of thyroid hyperactivity followed by thyroid hyperactivity. In view of this situation large doses of oestrin are indicated The period of necessary treatment is limited in this group, however, to a shorter time, usually not over two years

In addition to the foregoing states, Cawadias recognizes another group with osteoarthritic and fibrositic complaints which are due to a deficiency in the anterior-pituitary and diencephalon-pituitary system Oestrin is a secondary consideration in these patients and oestrin, when used, should be administered in conservative dosages

The recognition of the rôle of hypo-ovarianism as a cause of rheumatic disorders is important Clear differentiation of the etiological mechanism involved is essential to rational therapy Cawadias concludes that oestrin is a valuable agent in treatment and must be employed in conjunction with appropriate physical and other general agencies

Surgery—Following the reports of Forbes, J. F. Mackenzie⁸ that hypertrophic arthritis in the hip undergoes improvement following fracture of the

femur, G. D. Kersley,⁹ records observations upon the use of *therapeutic bone drilling*. The procedure though recorded as simple is applied chiefly to otherwise refractory cases. The operative procedure consists in the removal under local anesthesia of a portion of bone with a cork borer. The removed tissue is subjected to microscopic and chemical analysis.

In the 20 reported cases the operation was conducted only upon the more accessible bones, *viz*, those of the hands, wrists, elbows, knees and feet. Among 6 cases of gout, one experienced both local and general improvement which was lasting Four cases presented a delayed general improvement which was attributed to the effects of the spa regimen rather than to the operation One case showed no improvement. Among 11 cases of atrophic (rheumatoid) arthritis 5 showed marked immediate local improvement, 4 of whom maintained their betterment One patient showed general improvement and 5 none The beneficial results in this group were attributed chiefly to the rest rather than to the operation itself

The most encouraging results appeared in the hypertrophics, all of whom (3) showed immediate, marked, and permanent improvement The favorable results are attributed to improvement in circulation which provides better nutrition to the bone. In addition, there is a physiological stimulus to the bone cells An additional factor of possible importance is the reduction of interosseous tension associated with the removal of bone tissue

In view of these results it appears that the procedure is only to be recommended in hypertrophic arthritis and then only after rest alone has been found inadequate to cope with the situation.

The arthritis associated with ulcerative colitis may usually be successfully treated medically. S. J. Campbell,¹⁰ reports a case successfully treated by *colectomy*. The patient was markedly malnourished. Medical therapy was unsuccessful. The double effect of the malabsorption of essential dietary materials and the focus of infection constituted by the disordered colon was responsible for the patient's condition. After the removal of the colon coupled with administration of an optimal diet the patient recovered.

Drugs—Gold salts have been more widely used during the past year in the treatment of arthritis. A number of papers have appeared detailing the methods and results of therapy with these agents. While no account has been presented which indicates the mechanism underlying the alleged benefits, there seems to be a widely held view that gold salts do accomplish positive results in a certain number of cases. A conservative report by P. Ellman, and J. S. Lawrence,¹¹ presents an assessment of its value with some control experiments. The patients studied had been under observation for at least 1 year before initiating the gold therapy. To minimize risks of complications no patients were included who showed a previous history of purpura. No subjects were used who were unable to concentrate a urine to a specific gravity of at least 1.020. By the same token, no patients were subjected to gold therapy who showed albuminuria. The dosage used is similar to that noted earlier, *viz.*, $\frac{1}{16}$ grain (0.01 Gm.) per dose to a total quantity of $37\frac{1}{2}$ grains (2.5 Gm.) during a period of 6 weeks.

Of 60 cases, 50 per cent were made inactive, 80 per cent showed reduction of joint swelling and diminution of pain. No roentgenographic evidence of alteration in the joints and bones was en-

countered. Objective evidence of systemic change was noted in the fact that 83 per cent showed return to normal sedimentation rate after the course of therapy. These data provide evidence that some significant responses follow the application of gold.

Certain toxic effects were occasionally noted including various sorts of exfoliative skin lesions. The renal complications are shown by the presence of casts of red cells and albumin in the urine. Hepatic involvement is shown by jaundice. The hematopoietic system may be damaged as shown by purpura hemorrhagica, aplastic anemia and agranulocytosis. Mucous membranes in states of toxicity show ulcerations. Stomatitis may appear. The central nervous system may become involved, but this is a rare complication. The psychic manifestations include asthma, melancholia and mania.

One of the additional effects of gold therapy is cited by C. L. Gaskings.¹² Gold salts produce a depressing effect on the level of blood platelets particularly when the initial level is low. These agents may induce a drop in the platelet count of as much as 50 per cent within 2 to 4 days. The average drop among 28 cases of atrophic arthritis during a period of 5 weeks, under gold treatment, was 48 per cent. This apparently large drop may be partially minimized by the fact that a drop of 20 per cent in the platelet level was noted in 5 normals and 4 atrophic arthritic subjects not treated with gold. Ordinarily the drop induced by gold is less when the initial level of platelets is high than when the platelet count is low. A drop to 250,000 or less is regarded as a danger signal.

In view of the risks it is evident that gold therapy should be instituted only under conditions where close check of the condition of the patient is available.

J. A. Key, H. Rosenfeld and O. E. Tjoflat¹³ record observations with the use of a gold salt, *sodium aurothiomalate*, in doses of $\frac{2}{5}$ to $1\frac{1}{2}$ grains (0.025 to 0.1 Gm.) at weekly intervals until 30 grains (2 Gm.) of myochrysin were administered to 70 patients with atrophic arthritis. Of this series 9 cases of spondylitis were not benefited. Of the series of 53 typical atrophic arthritics, 2 were worse, 6 not improved, 4 slightly improved, 13 moderately improved, 18 markedly improved and three "cured." Upon the basis of these observations the authors consider gold salts among the most valuable drugs in the treatment of atrophic arthritis. Accessory dietary factors including vitamin C, liver or stomach extracts and iron were given. These factors are regarded as possible protection against the toxic influence of gold.

A study conducted by H. C. Coggeshall and W. Bauer¹⁴ provides a basis for evaluating the use of *sulfanilamide* in the treatment of gonorrheal and atrophic arthritis. The treatment was conducted upon 14 cases of proved gonorrheal arthritis and 4 cases of probable gonorrheal arthritis, and upon 10 cases of typical atrophic arthritis during various stages of development. The daily dosage of the drug was estimated upon the basis of bodily weight, *viz.*, 2½ grams per pound (0.33 Gm. per kilogram) of body weight. If this quantity was administered in amounts of one-sixth of the total every 4 hours, the blood sulfanilamide level was maintained between 7 to 10 mg. per 100 ml. If higher levels of sulfanilamide in the blood were desired over half of the calculated dose for the 24 hours was administered as an initial dose. This was followed by a similar quantity in 4 hours. In each subsequent 4-hour period one-tenth of the calculated 24-hour dos-

age was administered. Under these conditions the levels of sulfanilamide in the blood reached 15 mg. per 100 ml. Administration, when continued for 2 weeks or longer, was associated with clear-cut evidence of influence upon certain strains of the gonococcus. Infected synovial fluids became sterile within 24 to 72 hours after starting therapy. The gonococcus disappeared from the genitourinary tract within the same period. The gonococcus complement fixation test either failed to become positive or rapidly became negative in most of the treated cases. The general clinical features were promptly and permanently cleared. The sedimentation rate returned to normal in those cases which presented early and marked clinical improvement. Emphasis is placed upon the desirability of the early institution of sulfanilamide therapy and upon the necessity for administration of large doses divided over short-time intervals in order to maintain fairly high levels of sulfanilamide in the blood. In marked contrast to the favorable results in gonorrheal arthritis the clinical course of the patients with atrophic arthritis was not affected. The sedimentation rate likewise remained unchanged.

Severe reactions were not noted in great frequency. Temporary cyanosis, and dyspnea related to alterations in electrolyte balance occurred. Slow progressive subclinical hemolytic anemia was encountered in 12 and leukopenia in 2 cases.

T. D. Jones¹⁵ reported that sulfanilamide not only failed to exert a beneficial effect on rheumatic fever in 58 cases but induced definite evidence of toxicity in 31 of these cases and therefore urged against the use of this drug in the patient severely ill with rheumatic fever.

The application of *radioactive materials* to the treatment of arthritic disorders dates from the time of their dis-

covery Exaggerated and unsupported claims have been made regarding the utility of these agents Few detailed clinical studies have been made, many reports having been based upon indiscriminate administration to sick patients without regard to a separate evaluation of results in terms of the type of disease While not providing a rationale of this form of therapy, the report of M. P. Weil, and F. Bach,¹⁶ provides clinical data worthy of consideration.

After extended use of radioactive materials of several kinds, Weil and Bach conclude that **thorium X** is perhaps the most desirable agent used to date Thorium X is administered in doses of about 100 micrograms once a week in a series of 8 injections Administration is made intravenously, intramuscularly and never intracutaneously No course of treatments is carried out with amounts exceeding a total of 800 micrograms. An interval of 12 to 18 months between series of injection is always provided for. The effect of the thorium X is attributed to the alpha rays emitted

In view of this fact, evaluation of dosage should be made in terms of electrostatic units Other radioactive substances produce alpha rays and many of these have been used Radium produces alpha, beta and gamma rays Radon, a gas, produces alpha radiation with a half period of 3.8 days In this respect radon is similar to thorium X which produces alpha rays with a half period of 3.6 days Other members of the thorium group are less suitable The thorium X is prepared by precipitating mesothorium from an aged solution with ammonia Under these conditions thorium X remains in the filtrate

The use of radioactive waters is, according to Weil and Bach, not uniformly effective. The action of radioactive agents appears to be somewhat comparable to

that of arsenic, thyroid, and roentgen radiation in so far as these produce in proper dosage a tonic and stimulating effect

Among the complications associated with the use of radioactive agents in rheumatics the following conditions have been encountered: Radiodermatitis; primary anemia, leukemia and bone necrosis Localized subcutaneous necrotic areas which later become calcified may follow cutaneous administration. Exacerbation of pre-existing psoriasis has been observed Minor complications in the form of fatigue, mild gastrointestinal disturbance, slight fever and increased stiffness are also encountered

According to Weil and Bach, thorium X is of doubtful value in hypertrophic (osteoarthritis) but distinctly valuable in atrophic (generalized inflammatory) and in gouty arthritis It is considered useful in cases presenting both psoriasis and atrophic arthritis (psoriatic rheumatism) It is regarded as of value in the late stages of atrophic spondylitis (spondylosis rhyzomelic) For the earlier stages of the latter, rest in bed, casts, gold salts and orthopedic exercises are recommended

In the light of the foregoing observations it appears that despite the occasional complication and lack of precise data regarding influence, radioactive agents merit a further therapeutic trial in those refractory cases which do not respond to the more conservative and usually effective measures

Pregnancy—The ameliorating effect of jaundice noted by P. S. Hench¹⁷ has been compared by him to the similar influence of pregnancy The observation is based upon a study of 22 women with 37 pregnancies. Twenty of the patients experienced striking, usually complete symptomatic relief during the period of pregnancy The only occasion when re-

lief was not noted in this group was an instance of tubal pregnancy. In 2 of the women pregnancy apparently exerted no beneficial effect. The influence usually appeared from the second month to the third month of gestation. The relief from symptoms was usually complete with respect to pain and stiffness. Reduction in articular swelling was usually almost complete.

The phenomenon was so striking to the patients that some, for therapeutic purposes, became pregnant. The relief from symptoms usually persisted about 1 month post partum. Occasionally the period of relief was longer. The average duration of relief for the series was 9.4 months. The presence or absence of lactation appeared to be without influence upon the time of return of symptoms. Some correlation with the time of return of menses to the return of symptoms was noted. The activity of the disease returned in 8 of the 20 cases, a slow return in 5, a rapid return in 4, in 1 progressively less severe after 4 pregnancies. No evident reason appears to explain the absence of relief in the 2 women who showed no remission of symptoms during pregnancy.

The phenomenon of relief has been noted by others earlier including Pemberton who stated in 1920 that "any critical observer can satisfy himself that the incidence of some conditions, such as pneumonia and pregnancy, may be followed by temporary improvement or entire surcease of symptoms in chronic arthritis." However, the explanation of the nature and mechanism of this influence is not yet at hand. Hench indicates that the ameliorating influence is suggestively similar to that seen in cases of jaundice. Both pregnancy and jaundice are assumed to involve physiologic states antagonistic to the continuation of articular diseases, particularly atrophic

arthritis. For economy of theory it is supposed that the common basis for such a state is the presence of a chemical substance. It is noted that close chemical relationships exist between cholesterol, ergosterol, certain sex hormones, and bile acids. Exploration of these common agents with respect to their therapeutic influence is regarded by Hench as a basis for progress in effective treatment.

X-rays—Van Dam⁴ reviews some of the methods employed in **x-ray treatment**. The action of x-rays may act by means of a sedative effect, reabsorbent effect, *i. e.*, reducing joint swelling, or by increasing the range of motion without gross change in appearance. The best results of this measure appear in cases of spinal involvement.

The usual procedure applies a penetrating ray of 180 kilovolts at 30 cm. focus from the skin, 110 to 130 R. per dose ($1\frac{1}{2}$ H. E. D.) to the large joints with $\frac{1}{2}$ mm. copper and 1 mm. aluminum filter. Another procedure employs softer rays, *e. g.*, 125 kilovolts at focus of 17 cm. 110 R. per dose using a filter of 0.3 mm. copper.

Therapy of Circulatory Disturbances—The rôle of circulatory disturbances in the production of some of the symptoms of arthritis and the influence of certain forms of treatment upon these deviations have been reviewed by R. Pemberton and C. W. Scull.¹⁸ The lay viewpoint which attributes many of the features of rheumatic disorders to disturbances in peripheral circulation is supported by a variety of more or less precise clinical and experimental data. The functional departures from normal are reflected in a tendency towards cold hands and feet, parasthesias, pale and cyanotic finger nails with a tendency toward undue sweating. Skin lesions arising from trophic disturbances frequently appear. It is probable that the

circulatory disturbances are induced by some agent or agencies which influence other systems. Regardless of the nature of the primary agency disturbing the circulation, important secondary consequences follow in the wake of it.

One conspicuous feature of the disease is the ready development of fatigue. The latter condition is currently regarded as an expression of an oxygen debt incurred by the tissues. This physiological deficit may be liquidated only by the provision of ample supplies of oxygen or by removal of the metabolites arising from oxygen deficiency. Either one or both of these depend upon the adequate flow of blood within the area. It is evident that such fatigued states could originally arise from deficient circulation. Even if arising from some other cause one therapeutic approach is to increase the circulation in the peripheral tissues. Direct observation of the flow of blood in the superficial cutaneous vessels lends credence to this possibility. Direct observations by Pemberton and Peirce revealed comparative stasis in only 2 per cent of normals but 29 per cent in active atrophics and 35 per cent in active hypertrophics. "intermittent" flow in 10 per cent of normals, in 54 per cent of atrophics, and 32 per cent of hypertrophics; slow rate in 12 per cent of normals, 44 per cent atrophics, 28 per cent of hypertrophics; narrow capillaries in 35 per cent of normals, 70 per cent of atrophics, 75 per cent of hypertrophics. These data show that there is a condition resembling partial constriction of the capillary blood vessels at the finger ends of many arthritics. The application of measures such as *massage*, *heat*, *exercise*, the administration of *aspirin*, the *injection of coffee*, increase the cutaneous blood flow. These measures often were followed by subjective relief of some symptoms.

These observations coupled with those data obtained by thermocouple measurements showing a decreased degree of vasomotor response following exposure to cold, support the view that significant disturbances are present in the finer circulation in the peripheral tissues of the arthritic. It is to be noted that the low grade edema of the arthritic in part is to be attributed to local circulatory dysfunction which gives rise to abnormal fluid distribution.

Circumstantial evidence suggests that some features of the bony and articular pathology of the arthritic may be referred to circulatory factors in these regions. The general vascular changes which develop during the period of increasing age undoubtedly subject the tissues and organs to a certain degree of embarrassment by virtue of the diminished supply of nutrient material which reaches them. The ends of bones are supplied with small vessels which are the peripheral portion of the vascular supply of bone and such regions might be expected to suffer relatively early from the effects of diminished blood flow. In hypertrophic arthritis the degenerative changes may be referable to such primary disturbances in the vascular system. Similarly the bone and muscular atrophy of atrophic arthritis may be secondary consequences of primarily deranged local circulation with consequent impairment of tissue nutrition.

In addition to the cutaneous and skeletal circulatory disturbances many arthritics are certainly subject to some changes in blood flow in the viscera. Visceroptosis appears to involve a certain degree of pooling or stagnation of blood in the splanchnic area. The bed-ridden or chair-ridden arthritic is further handicapped by a lack of normal support to venous and lymphatic circulation

due to deficiency of full movements of the diaphragm.

All of the foregoing deviations are susceptible to correction in a certain degree by obvious procedures. Measures, such as *rest in bed, heat, massage, postural exercises*, directed toward such deviations contribute materially toward the well being of the arthritic and should therefore be included as a part of the well-rounded approach to the ill individual as a whole.

General Therapy—The treatment of chronic atrophic arthritis requires a comprehensive and well-balanced regimen. A recent evaluation of several of the important features of such a regimen has been presented by H. E. Thompson, B. L. Wyatt and R. A. Hicks.¹⁰ This study is based upon admission data on 343 patients together with follow-up analysis on 274 patients. It is worthy of note that while the incidence is greatest between the third and fourth decade, no age group is exempt. Focal infection was present in 57 per cent of 198 patients. The site of involvement in the order of incidence appears as follows: Thorax or pharynx; sinuses, gingiva, tonsils or remnants, teeth, and urinary tract and with less than 10 per cent incidence in the lower respiratory tract, female pelvis, prostate, gall bladder, colon. Particular attention is directed to the fact that careful examination is required to detect infection in the gingiva but that such search is often fruitful.

The judicious *removal of focal infection* is considered important despite the expressions often made of a contrary opinion. It is admitted that such removal may not always constitute a "specific" influence but it is felt that the constitutional improvement often associated with such therapy is at least partly dependent upon this measure. The prognosis for

patients suitable for treatment of focal infection is often better than for persons in whom no focal infection is found.

Both local and general rest is regarded as a necessary foundation of treatment. During the acute stage bed rest is required. The joints are kept as nearly as possible in a position of extension and function. Such rest is modified by putting joints through the painless range of motion several times per day. After the acute stages are passed gradual exercises are permitted. All kinds of activity are kept within the limits of fatigue.

Physical therapy, including *heat, light* and *massage* is recommended according to the various requirements of the individual. It is to be noted that hyperpyrexia is of little benefit to the atrophic arthritic.

Dietetics are regarded as important. No single dietetic prescription is applicable to all patients. The underweight patient is placed upon a *high calorie, low starch, high vitamin diet* supplemented by *milk* and *cream*. Vitamin B supplements are provided in the form of *wheat germ*. Attention is called to the fact that persons who can tolerate a reduced caloric intake often show a remarkable diminution of doughy swelling. Similar reduction follows starvation, nausea and vomiting, diarrhea and ether anesthesia. Factors other than the obvious corollaries associated with under and overweight are to be considered in relation to the nutritional adjustment.

Blood transfusions of about 10 ml per kg. of body weight administered at intervals of 2 to 6 weeks are considered useful. The clinical improvement is apparently not due to the increase in red blood cell count alone. Improvement is usually, though not always, paralleled by a decrease in the sedimentation rate.

Transfusions are recommended for patients who are resistant to other forms of treatment such as those who are markedly debilitated and present persistent and severe secondary anemia.

Climatic agents including *warm dry air* together with *heliotherapy* are considered valuable constitutional measures. Graduated exposure to sunlight is recommended. *Such exposure is contraindicated* in the presence of fever, the appearance reactions and complicating conditions such as tuberculosis, myocardial disease, general debilitation and old age.

Orthopedic care in the prevention of deformities is carried out with the use of *rest, splints, physical therapy* and *exercise*. These measures are applied judiciously over the entire period of management. The correction of deformities is approached first with respect to such measures as traction, cast wedging, adjustable splints and manipulation. Extreme conservatism is advised in the application of the latter. Operative procedures may be required but are generally deferred until the activity of the disease is reduced to a minimum. Such measures include *synovectomy, arthroplasty, capsulotomy, arthrotomy, osteotomy* and *arthrodesis*.

Antigens and *vaccines* may be used according to the authors with greatest propriety when the agglutination titres are low and the sedimentation rates high.

Drugs with the exception of *salicylates, iron*, and possibly massive doses of *vitamin D* are regarded as of slight value. Among the toxic drugs and those considered to be of doubtful value the authors cite the gold salts, sulfur, chaulmoogra oil, arsenicals, cinchophen, colchicine, snake venom and bee sting extracts.

The results of treatment over an average period of time indicate that 76 per

cent of the patients experienced marked or moderate improvement which persisted in the following years. Emphasis is placed upon the fact that successful treatment demands the use of a variety of factors, many of which must be conducted over a considerable period of time before the maximum benefit of such therapeutic agencies can be derived.

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CARDIOVASCULAR SYSTEM

By ALBERT W. BROMER, A.B., M.D.

Introduction — During the 2 years just passed there has been increased appreciation of the importance of nutritional factors in the etiology of cardiovascular disturbances; the significance of various deviations in the precordial leads of the electrocardiogram has become better understood; and the importance of psychotherapy in the treatment of essential hypertension, the relative therapeutic efficacy of various whole leaf and glucoside preparations of digitalis, and the value of intermittent venous compression in the treatment of peripheral vascular disease have been demonstrated, respectively.

Beriberi is looked upon usually as a disease of rice-eating people of the Orient, due to *deficiency of vitamin B₁*; but recently S. Weiss and R. W. Wilkins have directed attention to its not infrequent incidence in the United States among individuals suffering general malnutrition, chronic alcoholism with or without polyneuritis, pellagra, neuritis of pregnancy, and diabetes. This discovery arose with recognition of the fact that certain types of neuritis are related to nutritional disturbances, particularly lack of vitamin B. The patients usually are well nourished, with caloric intake adequate or more than adequate, but with an estimated vitamin B (B_1) intake less than that indicated by Cowgill as liable to produce polyneuritis. Many of the patients also have symptoms of pellagra, and a few, scurvy. The most common cardiovascular symptoms are dyspnea on exertion, associated with palpitation, tachycardia, and embryocardia; the heart may be normal in size or enlarged; signs of pulmonary congestion are frequently present, with cloudiness of the lung fields

on x-ray examination; the arterial pressure is usually normal with a tendency to increased pulse pressure; edema, either dependent or diffuse, is frequently present. Some patients show improvement on a deficient diet when simply put to bed; others may show aggravation of symptoms or even fatal collapse when kept in bed and on a deficient or even a normal diet. Diets rich in vitamins (particularly B), extracts rich in B_1 , and crystalline B_1 are beneficial. In some instances, digitalis and diuretics prove of benefit.

Absence of the initial positive deflection in the *precordial lead* of the electrocardiogram has been found by A. M. Master, S. Dack, H. H. Kalter and H. L. Jaffe to be associated with recent or old coronary thrombosis and anterior wall infarction in $\frac{2}{3}$ of 120 patients with this electrocardiographic finding; in $\frac{1}{5}$ of the instances there was present coronary artery disease alone, with or without hypertension (possibly cases of unrecognized myocardial infarction); and in the remaining 14 cases—all without evidence of myocardial infarction—the diagnoses were miscellaneous, *viz.*, acute and chronic glomerulonephritis, rheumatic and syphilitic valve disease, pneumothorax, Graves' disease, and acute myocarditis. Of 175 patients with a *small initial positive deflection* (2 mm or less), in only 13 was the heart presumably normal; the remainder suffered from coronary thrombosis (29 per cent), coronary artery disease with or without hypertension (37 per cent), rheumatic valvular disease (14 per cent), miscellaneous heart involvement (12 per cent). A small initial positive deflection, therefore, is almost as significant as none

As stated by D. Riesman, the variability—the labileness—of the blood pressure and the absence of structural (inflammatory or degenerative) changes in the arterioles in patients dying in the early stages suggest that spastic constriction of the arterioles is the likely cause of *essential hypertension*. The presence in hypertension of an *intrinsic vascular hypertonus*—on which normal vasomotor activity is superimposed—has been demonstrated by M. Prinzmetal and C. Wilson.

The treatment of essential hypertension is in large part *psychologic*. Many hypertensive patients overwork, overeat, undersleep and oversmoke, all of which departures from normal must be corrected. The man who takes to bed with him the “cares that infest the day” must be educated to a better habit. Exercise within reasonable limits is permissible. There is no specific drug that will permanently lower arterial blood pressure; the best results are obtained with sedatives, particularly the barbituric acid group. In regard to surgical operations for the cure of hypertension, reports have not been particularly impressive; however, as mentioned by Riesman, there is a possibility that some surgical method may be found that can be looked upon as curative.

Class instruction in the treatment of essential hypertension has met with considerable success in the Medical Clinic at the Boston Dispensary. Suggestion and psychotherapy form the basis of the method, but attention also is given to medical care and diet. The relatively benign course of essential hypertension is stressed, and the importance of physical and nervous strain in the development of symptoms is emphasized. At each class meeting the importance of regular and systematic relaxation is stressed. There is a 5-minute relaxation

period at each meeting; and “relaxation exercise” is practiced 1, 2, or 3 times daily during the week. The uniformity with which patients report feeling fine, when formerly a variety of symptoms were present, testifies to a new mental attitude. Some patients have shown no striking change in the blood pressure level, but in two-thirds of those who have made 3 or 4 visits to the class, a fall in pressure from 18 to 46 mm. of mercury has been observed.

A 6-year clinical study by W. D. Stroud and coworkers of 6 *digitalis* preparations, *viz*, (a) whole leaf tablets of digitalis prepared by the American Heart Association, (b) Burroughs, Wellcome & Company whole leaf tablets, (c) digalen, a preparation of “purified glucosides” (Hoffman-LaRoche, Inc.), (d) verodigen, a gitalin glucoside (Merck & Company), (e) digitaline (Nativelle), and (f) digoxin, a glucoside isolated from the leaves of *Digitalis lanata* (Burroughs, Wellcome & Company), showed all the preparations to be uniformly potent and efficacious, producing similar results when given orally in equivalent doses. A cat unit is represented by $\frac{1}{240}$ gram of verodigen, by $\frac{1}{600}$ gram of digitaline (Nativelle), and by $\frac{1}{160}$ gram of digoxin. There was no evidence that the glucoside preparations, when given by mouth, were quicker in action, more efficient, more prolonged in action, or less toxic than standardized whole digitalis leaves.

A clinical study by F. L. Chamberlain and R. L. Levy has shown *urginin*, a preparation of squill—consisting of a mixture in approximately equal proportions of 2 of the active, water-insoluble glucosides, crystalline scillonin A and amorphous scillonin B—to be an effective cardiac remedy. Urganin, however, offers no advantages over digitalis in the treatment of myocardial insufficiency.

Alternating suction and pressure holds a certain place in the treatment of *peripheral vascular disease*, but it has not proved superior to various other methods of therapy. Relief of *vasospasm* by measures such as *increased environmental temperature*, *fever therapy*, *anesthesia*, or *vasodilating drugs* is of importance in conjunction with its use. G. de Takats, F. K. Hick, and J. S. Coulter have called attention to the fact that the alternating suction and pressure apparatus causes a marked compression of the thigh—with venous compression—which probably is a considerable factor in the resulting benefit. However, in all probability vascular massage of the skin through the partial release of the cutaneous vessels from atmospheric pressure in alternating suction and pressure may have reflectoric circulatory effects on deeper structures.

The value of *intermittent venous compression* (based on the phenomenon of "reactive hyperemia") in the treatment of peripheral vascular disease recently has been demonstrated by W. S. Collens and N. D. Wilkensky. In its application de Takats and his coworkers have adopted the following triphasic cycle: (a) Elevation of the leg by means of a pulley arrangement, (b) venous compression (with a wide 8-inch cuff conically shaped to fit the thigh) while the leg is still elevated, and (c) horizontal position followed by release. The amount of venous compression varies between 90 and 60 mm. of mercury, in the absence of edema, cyanosis, ulceration and gangrene; when the latter conditions are present, 40 mm. of mercury is not exceeded at first. The duration of venous compression is determined by the appearance of a definite rubor which occurs in from 1 to 2 minutes when pressures of from 60 to 90 mm. are used. Two minutes of compression should be fol-

lowed by 4 minutes of release (3 minutes in the horizontal position and 1 minute in the elevation position). When the circulatory embarrassment is more pronounced, 1 minute of compression will readily produce a rubor and is followed by 1 minute release and 1 minute elevation, a cycle of 3 minutes. Ordinarily 30 minutes of this vascular exercise in the morning and 30 minutes in the evening are prescribed. Spreading infection, thrombophlebitis, and widespread arteriolar destruction are contraindications to the use of intermittent venous hyperemia.

ANGINA PECTORIS

Treatment by Improving the Movements of the Diaphragm

Relief of anginal pain through improvement of the movements of the diaphragm (presumably acting through more adequate filling of the heart and coronary vessels), effected by use of an *elastic abdominal support* supplemented by *dietary restriction*, has been reported by W. J. Kerr.¹ The patients were of the apoplectic type—with florid complexion and moderate or marked corpulency; the majority were in the sixth or seventh decade of life and a small number were in the fifth decade; all complained of *orthostatic dyspnea*, i. e., dyspnea only in the upright position.

All the patients had marked lumbar lordosis, moderate or marked upper thoracic kyphosis, and an increased cervical lordosis. The exaggerated curves of the spinal column assisted the individual to "get under" the great weight of the protuberant abdomen; the lower ribs were in the inspiratory position and the upper ribs in front were approximated and relatively fixed in the expiratory position. Fluoroscopic examination in the upright

position showed the diaphragm to be 1 or 2 interspaces below the normal position; in ordinary breathing in the upright position the movements were limited, but when supine the diaphragm had a much greater excursion. It was assumed that the abdominal viscera together with the increased accumulation of fat served as a counterweight suspended from the diaphragm. When the individual was in the upright position, this weight interfered with the normal rise of the diaphragm during expiration; but in the supine position it caused the diaphragm to rise higher in the chest during expiration and acted as an aid to respiration. The relaxation of the fascial sheet extending from the cervical fascia to the lumbar spine, and including the pericardium and central tendons of the diaphragm, also interfered with the normal movements of the diaphragm. It was apparent that the diaphragm, handicapped by the counterweight, the flared lower ribs and the relaxed anchorages, was unable to maintain the tidal air at the normal level, which fact probably explained the orthostatic dyspnea, and the resulting pulmonary emphysema seemed to be the cause of moderate polycythemia.

In approximately 100 patients treated during the past 4 years, the results have been gratifying. The abdominal belt^{2, 3} used is sufficiently strong to lift the counterweight, and also is elastic to permit expansion during inspiration and to assist in elevating the diaphragm during expiration. By means of diet, the patient's weight is reduced closer to normal over a period of several weeks or months. As relief begins almost at once after the elastic belt is properly applied, it is not caused by reduction in weight. However the same result might probably be obtained by reducing the counterweight in the abdomen through general reduction in body weight, but only after weeks or

months of dietary restriction. The patients have been able to dispense with vasodilator drugs and there has been a definite increase in tolerance for exercise without anginal pain. A lighter type of elastic belt has been found to afford complete relief to persons of slender build with the same syndrome.

Restored function of the diaphragm is believed the important factor in the results obtained. In breathing, the movements of the diaphragm aid the return of blood to the heart through alternating changes in the intrapleural and intra-abdominal pressures. In the upright posture the relatively inactive diaphragm may impede materially the flow of blood from the abdominal viscera and the lower part of the body.

Digitalis in Angina Pectoris

To determine whether or not digitalis in therapeutic doses is liable to provoke pain by a specific action on the heart and blood vessels in persons with angina pectoris, the effect of the drug has been carefully observed by H. Gold, H. Otto, N. T. Kwit and H. Satchwell⁴ in a group of 120 patients with angina pectoris. The criteria used in the selection of patients were: Evidence of organic heart disease, absence of signs of congestion, cardiac pain on effort, doing very little or no physical work, and faithful co-operation. A total of 243 courses of treatment with fairly large daily doses of digitalis (from 3 to 10 grams or 0.2 to 0.6 Gm.) was given, each course lasting an average of 11 weeks and being alternated with a course of a placebo of lactose or some other agent with the form, taste and color of the drug masked. Nearly $\frac{1}{2}$ of all the patients reported a change from their habitual status after the first course of treatment with digitalis, in about 15 per cent the pain was increased; in about 30 per cent it was

TABLE 1
PRECIPITATING CAUSES OF CONGESTIVE HEART FAILURE

Cause	Incidence	Number Compensated with Treatment	Number Not Compensated with Treatment
Gradual onset (cause unknown)	47	1	46
Infection	18	12	6
Exercise	20	14	6
Pregnancy	5	3	2
Sudden rise in blood pressure	2	2	0
Sudden onset (cause unknown)	2	2	0
Psychic trauma	2	1	1
Hemorrhage	2	1	1
Surgical shock	2	1	1
Coitus	2	2	0
Heavy meal	1	1	0
Alcoholism	1	1	0
Total ..	104	41	63

diminished. Quite similar results were obtained during the use of a placebo.

In the final analysis, the 120 cases fell into 4 types: (a) Those in which the habitual status remained constant and apparently uninfluenced by *any* drug that was used (10 per cent), (b) those in which temporary departures from the habitual status were always in the direction of increased pain (33 per cent), (c) those in which temporary departures were always in the direction of improvement (20 per cent), and (d) those in which the condition fluctuated markedly in both directions (61.7 per cent). In no instance was there unequivocal evidence that digitalis had intensified the cardiac pain, even though dosage was so large in about 38 per cent of the cases as to cause toxic symptoms.

The conclusion is drawn that in angina pectoris without congestive failure the likelihood is negligible that digitalis will increase or diminish cardiac pain by direct action on the circulation. It must be borne in mind, however, that cardiac pain occurring in the course of myocardial failure with congestion often is relieved by digitalis through improvement in circulatory efficiency.

CONGESTIVE HEART FAILURE

Precipitating Causes of Congestive Heart Failure—The importance of added strain in the precipitation of congestive heart failure has long been recognized. In a study of W. A. Sode-man and G. E. Burch⁵ of 100 consecutive cases of congestive heart failure, a definite precipitating cause was demonstrable in 55 (52.9 per cent) of 104 attacks. (In 3 individuals a different precipitating cause was apparent in subsequent attacks.) The *underlying* causes of failure were as follows: Hypertension and arteriosclerosis, separately or in combination, accounted for over 75 per cent of the group, syphilis for 10 per cent, rheumatic fever for 7 per cent, and congenital anomalies for 1 per cent. The *precipitating* causes of congestive failure were distributed as follows (Table 1). Exercise in 20 instances, infection in 18 (upper respiratory tract, 15; acute gastroenteritis, 1; acute bacillary dysentery, 1; erysipelas, 1); pregnancy, 5; surgical shock, 2; coitus, 2; sudden rise in blood pressure, 2; psychic trauma, 2; hemorrhage, 2; heavy meal, 1, and alcoholism, 1. In 2 patients the onset was acute with-

out a definitely known cause but was probably due to a sudden rise in blood pressure. In 40 (75 per cent) of the patients in whom precipitating causes were demonstrable, circulatory efficiency was established rapidly and sufficiently under treatment to render it possible for the individual to carry on usual activity, 14 failed to show improvement to that extent, and 3 could not be followed.

In the group of 47 patients with congestive failure of gradual onset without demonstrable cause, 46 were unable with treatment to recover circulatory efficiency of sufficient degree to carry on minimal normal activity. Such patients usually developed evening edema which became progressively worse for a varying period of time until they were bedridden; apparently there was no forewarning of the progressive diminution in cardiac reserve until it was so diminished that even minimal activity exceeded it. If a patient of this type had warning of diminishing cardiac reserve by a precipitating factor before this limit was reached, he probably would have reacted to treatment and would have been able to adjust his activity to meet his existing cardiac reserve, and, in addition, treatment of any correctible etiological factor could have been instituted to prevent further cardiac damage. With the exception of patients with syphilitic heart disease with aortic regurgitation, who showed an inability to regain circulatory efficiency regardless of the precipitating cause, the etiological diagnosis was not found to be significant.

(Understanding of the precipitating causes of congestive heart failure is of the greatest importance in the treatment of patients with heart disease who have not yet developed myocardial failure. Postponement of the onset of failure can be influenced more by the control of these factors than by any means other than checking the advance of the underlying causative disease. But, unfortunately, many of the

underlying causes of heart disease do not respond to treatment—EDITOR.)

Causes of Death in Congestive Heart Failure—The factors (circulatory or noncirculatory) which actually produce death in congestive heart failure, and the effect on these factors of modern methods of treatment have been investigated by R. H. Williams and F. Rainey⁶ in a study of 2 groups of patients with congestive heart failure, subjected to postmortem examination during the years 1926-1930 and 1931-1935, respectively, at the Vanderbilt University Hospital. There were 81 cases in the 1926-1930 group, and 104 in the 1931-1935 group. The vascular diseases constituted about 60 per cent; rheumatic and syphilitic diseases, each about 15 per cent of the cases, and others about 10 per cent. In the 1931-1935 series there was a relatively greater incidence of cases in the hypertensive and the rheumatic groups, and a slight decrease in the other groups.

The only significant difference in the treatment of the 2 groups of cases was the more extensive use of *diuretics* which began in 1930, other therapeutic measures, such as *sedatives*, *digitalis*, fluid intake, diet, and activity, were essentially the same throughout the 10-year period. In the 1931-1935 group, edema was treated by the use of *xanthine diuretics* for 2 or 3 days each week, with or without *salyrgan*. The latter was employed freely in all cases except those exhibiting evidence of impaired renal function.

The median duration of life after the onset of congestive symptoms was 11 months for the 1926-1930 group, and 18 months for the 1931-1935 group. The average age at death was between 35 and 45 years for all types of heart disease except the arteriosclerotic, in which it was about 65 years; these figures in general were lower for the 1931-1935

group than for the 1926-1930 group. Death from congestive heart failure and from pulmonary embolism and infarction distinctly decreased in frequency during the period from 1931-1935. During this same period pneumonia, both as a primary and supplementary cause of death, increased in frequency, particularly in patients with arteriosclerotic heart disease. It is noteworthy that in syphilitic aortic insufficiency congestive failure accounted for 50 per cent of the deaths in 1926-1930, whereas it accounted for only 17 per cent in 1931-1935; in the arteriosclerotic type it accounted for 15 per cent in the first period and for none in the latter. The frequent occurrence of pulmonary infarction and pneumonia as supplementary causes of death emphasizes the need of greater attention to the problem of the prevention and treatment of respiratory infections in patients with congestive heart failure, and possibly might indicate the importance of avoiding a too lengthy initial period of complete bed rest.

Intensive treatment with salyrgan did not increase the incidence of uremia in patients without hypertension. However, 50 per cent of the patients in the 1931-1935 group who had hypertensive heart disease died of uremia, as compared with 30 per cent in the 1926-1930 group, most of these patients had either malignant or benign nephrosclerosis. It seems probable that the better control of edema in these patients in the 1931-1935 group protected a certain number from early cardiac death and allowed progression of the degenerative changes in the kidney. It is also possible that in subjects with occult renal injury the mercurial diuretic may have caused further damage to the kidneys.

Immediate Effect of Mercurial Diuretics on Vital Capacity of the Lungs — To determine the value of

diuretics in improving respiratory function in heart failure, a group of 9 patients with congestive heart failure, with breathlessness but with no evidence of peripheral edema or with edema only moderate in degree, has been studied by J. B. Alsever and S. A. Levine.⁷ In most instances the diuretic used was 1 or 2 cc. of mercupurin, administered intravenously; in a few cases a similar amount of salyrgan or a mercupurin suppository was given. All the patients were under bed care in the hospital, had been digitalized, and generally were taking ammonium chloride. In every case, definite improvement in the respiratory function, with amelioration of subjective symptoms, took place 24 hours after the diuretic was given. The degree of moisture at the bases of the lungs diminished, as evidenced by the absence of râles, the amount of dullness or the character of the breath sounds; and the vital capacity of the lungs showed an average increase of 290 cc.

The beneficial effect of mercurial diuretics on the factor of dyspnea alone in heart failure very likely results from the extraction of fluid from the engorged capillary bed of the lungs, with consequent increase in the amount of the remaining air spaces and in the capacity for oxygenation of the blood. Experimental studies have shown that the artificial production of pulmonary congestion causes dyspnea and an increase in the volume of blood in the lungs, and F. Parker, Jr., and S. Weiss⁸ have directed attention to the fact that the capillaries of the lungs in cases of mitral stenosis are markedly dilated, so that red blood cells within the center of the stream have very little opportunity to absorb oxygen from the alveoli, whereas in the normal lung red cells pass in single rows, being directly opposed to the alveolar epithelium, and also considerable pericapillary

edema is present in mitral stenosis. In addition, there is evidence to show that the total blood volume is increased in heart failure, and that part of the increase manifests itself in passive congestion in the lungs; and recently it has been demonstrated by W. A. Evans, Jr., and J. G. Gibson, 2nd,⁹ that a diuresis in edematous dogs is accompanied by a sharp decrease in blood volume.

Rôle of Rest and Exercise in Congestive Heart Failure—With a critique of exercise as a therapeutic measure, a program of rest treatment for use in congestive heart failure has been presented by D. Davis.¹⁰ From 1900 to 1930 most clinicians recommended both rest and exercise in the treatment of congestive heart failure, but during the past decade a smaller number have stressed exercise in convalescence, although very few mention how long rest should continue. An exception, however, is Sir Thomas Lewis¹¹ who states that 6 to 8 weeks of bed rest is rarely sufficient, and that 3 to 6 months is desirable.

The analogy to skeletal muscle is partly responsible for adherence to the idea that exercise may improve a weakened myocardium. It must be borne in mind, however, that heart muscle has a structure and function that is in some respects decidedly different from that of skeletal muscle, and also that in the analogy the response of a healthy structure is compared with the response of one that is diseased.

In a study by D. Davis and H. L. Blumgart¹² it has been pointed out that myocardial failure in arteriosclerotic heart disease is due primarily to disease of the coronary vessels. If the coronary vessels are already so diseased that it is not possible to accommodate the normal requirements of the myocardium, they obviously will not be able to satisfy

the requirements under the conditions of exercise, and further damage to the structure is inevitable. It is difficult also to understand how exercise might be beneficial in other diseases of the myocardium. For example, hypertensive hearts are characterized by hypertrophy of the muscle fibers, and recently J. T. Wearn¹³ has called attention to the fact that the hypertrophied heart is less efficient because its capillary blood supply is relatively reduced.

Studies purporting to demonstrate improvement resulting from exercise either fail to do so or deal with conditions other than heart failure, *e g.*, obesity with dyspnea on exertion, compensated heart disease (such as rheumatic heart disease before failure has occurred), and psychoneurosis with symptoms suggesting circulatory insufficiency. The manifestations of circulatory insufficiency occasionally observed in elderly patients after weeks of confinement to bed because of some medical or surgical condition are of similar origin as the weakness which occurs when a young individual with a normal heart is confined to bed for several weeks. Dyspnea and weakness appear on the slightest attempt to increase activity beyond a certain limit, and only after weeks of gradually increasing activity is the previous capacity restored. This adjustment may be partly related to adjustments in coronary circulation, which must attend the increase in cardiac work, and elderly individuals with a narrowed coronary bed probably require more time to make the adjustment. See PROLONGED RECUMBENCY AS CONTRIBUTORY CAUSE OF DEATH.

To determine the importance of prolonged rest, the results of such regimen in 11 cases have been compared with a control group of 50 unselected patients with hospital admissions. Seven of the 11 cases who received prolonged rest

TABLE 2
REQUIREMENTS OF BED REST IN RELATION TO
DURATION OF CARDIAC FAILURE

Duration of Cardiac Failure Weeks	THERAPEUTIC BED REST		Prophylactic Bed Rest with Bathroom and Table Privileges Weeks
	Minimal Weeks	Desirable Weeks	
2 or less	12	16	1 out of 8
4	16	24	1 out of 6
8	32	48	1 out of 4
12	48	72	1 out of 3

were free of evidence of congestive heart failure for 3 or more years, and 3 have maintained good health for a period of 5 or more years. In the control group only 1 patient had an interval as long as 3½ years between the first and second attacks of failure, in another case 3 years elapsed between attacks, in 4, 2½ years; and in 5, 2 years.

In a program of rest treatment thought must be given to: (a) The duration of the initial period of *absolute rest* in bed, (b) the degree and character of reduced activity that must follow, and (c) the advisability of periodic prophylactic rest in bed. The patient with failure of severe degree, with signs and symptoms disappearing slowly, should rest in bed for a longer period than one less severely ill. After manifestations of failure have disappeared, there are 2 stages of improvement: (a) The period in which the cardiac reserve continues to increase to a certain optimum, and (b) a succeeding period (probably in the nature of organic repair) in which the gain in reserve—as measured by capacity to perform a given task—no longer shows very much change but in which the potential capacity of the heart is being increased. For example, in coronary disease improvement may be related to the better nutrition which follows the development of the better anastomotic circulation. As evidenced by a low cardiac output, a slow

velocity of circulation, and the inability to carry on any appreciable effort without symptoms, the point where manifestations of failure disappear may be a long way from the best possible recovery level. As the second period of recovery is far more significant in terms of the future, the rest phase should be at least twice and preferably 3 times that required for the first stage (Table 2).

The longer the initial period of bed rest, the greater the reduction in activity to be followed thereafter. In many instances engagement in some useful but less strenuous occupation is possible. In individuals with sedentary occupations the desired effect may be accomplished by increasing the sleep and bed-rest hours, eliminating stair climbing and walking, and spending the greater part of week-ends in bed. Prophylactic bed rest is of importance, in that the ultimate benefits to be obtained from rest are greater when it acts to prevent failure rather than after failure has appeared. The amount of such rest will vary with the degree of myocardial impairment.

PROLONGED RECUMBENCY AS A CONTRIBUTORY CAUSE OF DEATH

The mechanism by which prolonged recumbency may prove a contributory cause of death in elderly persons has been investigated by L. B. Laplace and J. T. Nicholson¹⁴ in a series of 34 patients confined to bed for orthopedic treatment. Thirty had fractured hips, and 4 underwent operations involving spinal arthrodesis; 27 were between 60 and 83 years of age, the remainder under 60 years; there were 13 males and 21 females. Confinement to bed appeared to be responsible for the deaths of 10 individuals, all of whom were over 65 years of age.

Careful clinical observations together with studies of the blood pressure, venous pressure, blood velocity, vital capacity, electrocardiogram, oscillometric index, complete blood count with Schilling index, urea nitrogen content of the blood, urinalysis, and in a limited number of cases the basal metabolism and urea clearance indicate that the malady induced by confinement to bed is analogous to shock prior to the stage of vasomotor collapse. Lessening of the number of movements made by an elderly person whose circulatory adaptation is impaired results in a progressive accumulation of blood in the venous capillaries and a progressive decrease in the volume of blood which circulates through the large vessels. Local anoxemia and consequent degeneration of the tissues lead to toxemia and to permanent capillary damage. There occurs a depression of the metabolic rate and of cardiorenal function, but there is usually no congestion of the type associated with primary heart failure.

The heart rate averaged between 70 and 100 and, except for tachycardia during fever or paroxysmal atricular fibrillation, showed no consistent tendency toward either acceleration or slowing. The blood pressure tended to fall slightly during the first 2 weeks, but on the whole it was well maintained, even when a patient had become practically moribund. Of the 10 patients who died, 9 showed either an initial fall of venous pressure or a consistently low level which did not exceed 3 cm. As a rule, the vital capacity of the lungs either remained unchanged or tended to become slightly increased. Decubitus ulcers occurred in all except 6 of the patients over 60 years of age who survived, and in all except 2 who died.

The likely cause of the predisposition of elderly individuals to this train of

events is the senile sclerotic changes in the small peripheral vessels. Such changes impair vasomotor function and hinder the circulatory readjustments which are made in response to changing needs of the body. Blood tends, therefore, to remain in the capillaries until forced into the veins by the contractions of the skeletal muscles.

The essential part of treatment is to order the patient out of bed before toxemia and permanent capillary damage have become firmly established. The time when this change occurs depends largely on the individual's previous health and on the severity of the malady for which he is being treated. The second, third and fourth weeks in the hospital formed the critical period for the fractured hip cases in this study. Certain patients who have been chronic invalids, accustomed to remaining in bed, or who possess the vascular efficiency of a younger individual may be confined without ill effect. However, the risk is always serious with persons over 65. The risk is particularly great in cases of senile heart disease; it is quite possible that many patients with such a condition who are put to bed die as a result of the contributory effect of this form of circulatory insufficiency rather than of their initial cardiac lesion.

Whenever an elderly patient must be confined to bed, alternative methods of maintaining muscular activity, such as *regular voluntary exercise, systematic deep breathing, massage and periodic shifting of position*, should be enacted. The patient should be kept mentally alert and cheerful—with some form of occupational therapy. Attention should be directed to the fluid intake, bowels and care of the skin. Drug therapy is of secondary value, but *coffee*, small amounts of *whiskey, strychnine* and *benzedrine* may prove helpful as

stimulants. For patients who have not responded to other forms of treatment, transfusion may be of benefit on the basis of its effectiveness in comparable cases of shock

DIAGNOSIS OF HEART DISEASE IN CHILDREN

The importance of roentgenographic examination of the frontal and the oblique planes of the heart in evaluating the significance of the precordial systolic murmur is called to attention by M. G. Wilson¹⁵ in a study of a group of children with organic heart disease, acquired and congenital, observed during the years 1916-1935 inclusive. Analysis of the physical examinations revealed that characteristic murmurs may become uncharacteristic or inconstant at times in the presence of abnormality of the cardiac silhouette and chamber enlargement. In only 11 per cent of 179 children with mitral insufficiency was a characteristic constant systolic murmur present at each examination. In 81 per cent the systolic murmur was at times indistinguishable from the so-called "benign systolic murmur." In about 60 per cent of 135 children with mitral insufficiency and mitral stenosis, the systolic murmur was characteristic, and in about 40 per cent uncharacteristic. In only about 35 per cent of 118 children with mitral insufficiency and mitral stenosis was the diastolic murmur constant and characteristic. In 65 per cent, when the murmur was inconstant or uncharacteristic, enlargement of the left auricle was demonstrable. In 36 per cent of 57 children with congenital heart disease, characteristic physical signs regressed.

Examination of the heart either by percussion or by mensuration of the frontal plane by roentgenologic examination will not reveal slight or moderate

enlargement in a large percentage of children with organic heart disease. The recognition of chamber enlargement, particularly by retrodisplacement of the esophagus by an enlarged left auricle in the right anterior oblique position, is of value in the diagnosis of mitral stenosis; and certain types of congenital heart disease can be recognized only on fluoroscopic examination. Since adequate roentgenologic examination is not as yet a routine procedure, it is apparent that slight and moderate enlargement of the heart may not always be recognized. The regression of characteristic physical signs of organic heart disease and the inability to recognize slight and moderate enlargement render it difficult to differentiate between a "benign systolic murmur" and a systolic murmur of organic heart disease

ELECTROCARDIOGRAPHY

Standardization of Precordial Leads

During the past few years since precordial leads have come into widespread use, there has been considerable confusion resulting from the lack of uniformity and precision in the technic and nomenclature employed by different observers. In view of this fact, committees of the American Heart Association and the Cardiac Society of Great Britain and Ireland¹⁶ have conferred and have made recommendations with reference to the routine use of a *single precordial lead*, as follows:

"1. It is recommended that those who employ a single precordial lead place the precordial electrode upon the extreme outer border of the apex beat, as determined by palpation. If the apex beat cannot be located satisfactorily by palpation the electrode may be placed in the fifth intercostal space just outside the left border of cardiac dullness, or just outside the left midclavicular line if percussion of the heart is unsatisfactory. Where precordial leads are

taken by a technical assistant, the position for the precordial electrode should be marked on the chest by the physician

"2 It is recommended that a single precordial lead in which the precordial electrode has the location specified in the preceding paragraph be known as Lead IV B when this electrode is paired with an electrode in the left interscapular region, Lead IV R when it is paired with an electrode on the right arm, Lead IV L when it is paired with an electrode on the left arm; Lead IV F when it is paired with an electrode on the left leg, and Lead IV T when it is paired with a central terminal connected through equal resistances of 5000 or more ohms to electrodes on each of the 3 extremities mentioned

"It is suggested that for all ordinary purposes Lead IV R or Lead IV F be employed. The latter lead should have the preference until it has been established that the former which is somewhat more convenient, is equivalent to the latter for all practical purposes, or yields results of equal value

"3 It is recommended that in taking the precordial leads specified, the galvanometer connections be made in such a way that relative positivity of the apical electrode is represented in the finished curve by an upward deflection (a deflection above the isopotential level) and relative negativity of the apical electrode by a downward deflection *

"It is urged that this convention be adhered to in the case of precordial leads other than those specified, and also in the case of all leads in which one electrode is placed much closer to the heart than the other. In other words, it shall be the standard convention in taking such leads to make the galvanometer connections in such a way that relative positivity of the electrode nearest the heart is represented by an upward deflection

4 It is recommended that with the galvanometer connections made as described in the

preceding paragraph, the deflections of precordial leads be designated by the symbols P, Q, R, S, and T, and that in the application of these symbols the same conventions be employed as in the case of the standard limb leads

"5 It is recommended that in taking precordial leads the electrocardiograph be so adjusted that a deflection of 1 cm in the finished record corresponds to a potential difference of 1 mv as in the case of the standard limb leads. Any reduction in sensitivity made necessary by very large deflections should be clearly indicated on the curve preferably by photographing the effect of introducing a potential difference of 1 mv into the galvanometer circuit

"6 It is recommended that the greatest dimension of the apical electrode employed in taking the leads specified in this report be 3 cm or less. A circular electrode between 2 cm and 3 cm in diameter should ordinarily be employed

"7 It is recommended that the terms Lead IV (R, F, etc.), apical lead, apex-leg lead, etc., be used henceforth only in connection with the leads specified in this report"

In a supplementary report,¹⁷ the Committee on Precordial Leads of the American Heart Association has made recommendations regarding *multiple precordial leads*

"In certain cases of intarction of the anterior wall of the heart, multiple precordial leads are required to establish the diagnosis. Such leads sometimes disclose abnormalities of the T-deflection, which would otherwise escape detection. In the differentiation of right from left bundle-branch block, and in the differentiation of right from left ventricular enlargement multiple precordial leads are indispensable

"When leads from 2 or more precordial points are employed, it is suggested that the precordial electrode be paired either with an electrode on the left leg or with a central terminal connected through equal resistances of 5000 or more ohms to electrodes on the right arm, left arm, and left leg. It is suggested further that in the first case the letters CF† followed by a subscript and in the second

* To make the galvanometer connections in such a way that positivity of the precordial electrode will produce an upward deflection in the finished record it is necessary to connect the left-hand wire to this electrode if the lead switch is on Lead I and to connect the left-leg wire to this electrode if the lead switch is on Lead II or Lead III. To take Lead IV F, connect the left-leg wire to the precordial electrode and the left-arm wire to the left-leg electrode and place the lead switch on Lead III. To take Lead IV R, connect the left-leg wire to the precordial electrode and the right-arm wire to the right-arm electrode and place the lead switch on Lead II

† Those who prefer to place the distant electrode on the right arm may indicate its position by using the letters CR followed by a subscript. When this electrode is placed on the left arm, the

case the letter V followed by a subscript be employed to designate such leads.

"The position of the precordial electrode shall be indicated by the subscript used according to the following plan. Subscript 1 shall be used for the right margin of the sternum; 2, for the left margin of the sternum; 3, for a line midway between the left margin of the sternum and the left midclavicular line; 4, for the left midclavicular line; 5, for the left anterior axillary line; and 6, for the left mid-axillary line. When the letters and subscripts specified are employed, it shall be understood that in the case of the sternal leads the precordial electrode has been placed in the fourth intercostal space and that in the case of the other leads it has been placed upon a line drawn from the left sternal margin in the fourth intercostal space to the outer border of the apex beat (or to a point at the junction of the midclavicular line and the fifth intercostal space) and continued around the left side of the chest at the level of the apex beat or of the junction mentioned‡.

"In the majority of cases there is no essential difference between the curves obtained when the precordial electrode is paired with an electrode on the left leg and those obtained when it is paired with a central terminal. Essential differences become increasingly common as the distance of the precordial electrode from the ventricular surface is increased."

Paroxysmal Bundle-Branch Block

Through the more frequent use of the electrocardiograph, cases of paroxysmal bundle-branch block are becoming a not uncommon finding. In an analysis of 71 cases of paroxysmal bundle-branch block

letters (L followed by a subscript may be used. The letters R, L, and F are used as abbreviations for right arm, left arm, and foot (left leg) respectively. The letter C is an abbreviation for chest, T for central terminal, and V for voltage. The last (V) is used only in connection with unipolar leads in which the central terminal is the indifferent point.

It will be noted that lead C₁ and Lead IV₁ (or lead CR₄ and Lead IV₂ R) may sometimes be identical. In the case of the latter (Lead IV₂ F or Lead IV₂ R), however, the precordial electrode is placed at the outer border of the cardiac apex regardless of the position of the apex with reference to the bony landmarks of the chest, whereas in the case of the former (lead C₁ or lead CR₄) this electrode is placed in the midclavicular line even when the cardiac apex is far to the left of this position.

(58 cases found reported in the literature and 13 new cases), made by W. J. Comeau, J. G. M. Hamilton and P. D. White,¹⁸ there was clear evidence of heart disease in 65 (35 males, 29 females, and 1 of unrecorded sex). With the exception of a few instances in which the intraventricular conduction time was over 0.10 second but under 0.12 second, the cases represented the classical form of bundle-branch block with Q-S intervals of 0.12 second or over. Six patients without other evidence of heart disease were excluded from the analysis, although the presence of paroxysmal bundle-branch block was considered in itself evidence of heart disease. Coronary or hypertensive heart disease was present in 44 patients, while chronic rheumatic heart disease was present in 6; in the remaining 15 patients the etiology of the heart disease was diphtheria in 4, thyrotoxicosis in 3, congenital in 1, and in 7 it was obscure. Left bundle-branch block (new nomenclature) was present in 60 of the 65 patients. In 25 patients moderate to severe heart failure was associated with the bundle-branch block.

In 6 cases in whom the effect of changes in the vagal tone was studied, single bundle-branch block complexes were obtained during vagal stimulation on 2 occasions in but 1 patient—which result indicates that increase in vagal tone does *not* produce sustained inhibition of bundle-branch conduction. Variations in vagal tone affect the conduction only by decreasing or increasing the cardiac rate to such an extent that the depressed branch becomes capable or incapable of transmitting impulses.

Although the precipitating factor of the bundle-branch block associated with coronary and hypertensive heart disease may be physiological in some instances, the fundamental cause is *organic heart disease* directly or indirectly affecting a

bundle-branch. Such cases are far more common than usually believed, and in some the intermittent block is undoubtedly the precursor of permanent branch block.

"It is not necessary that complete block exist in 1 branch in order that impulses be forced to travel through the opposite branch and the myocardium to reach the affected ventricle. Conduction by this pathway may be necessary when 1 branch only is depressed. So long as the conduction time through the damaged branch is greater than that through the intact branch plus the myocardial pathway between the 2 ventricles, the affected ventricle is activated by an impulse traveling through the latter channels, and bundle-branch block complexes result. Whenever the conduction time through the damaged branch passes the critical level and becomes shorter than that through the channel just mentioned, normal QRS complexes appear. It is therefore apparent that if conduction through the affected branch is close to this critical zone small changes in the conductivity of the depressed branch result in sudden and complete changes in the form of the ventricular complexes. Such small changes in conductivity result, for example, from the increase or decrease in diastolic rest due to slight alterations in heart rate."

Wide QRS complexes with short P-R intervals, which are of no serious significance, must be differentiated from the type just described. The short P-R interval type was found by L. Wolff, J. Parkinson and P. D. White¹⁹ (1930) to occur usually in young persons, without other evidence of heart disease, prone to attacks of paroxysmal auricular tachycardia, flutter or fibrillation. A reversion to the normal form may take place spontaneously, during the paroxysmal tachycardia, after exercise, or after the administration of atropine or quinidine. According to M. Holzmänn and D. Scherf²⁰ and C. C. Wolfarth and F. C. Wood,²¹ the abnormal ventricular complex does not represent a block in a bundle branch, but is due to the early arrival of an auricular impulse in 1 ventricle by way

of a short-circuiting bundle, such as a bundle of Kent.

In addition, among the inconsequential cases of bundle-branch block, there should be included the rare cases with no apparent cardiovascular disease in whom bundle-branch block manifests itself after a prolonged period of paroxysmal tachycardia. Although such finding is interpreted as indicating fatigue of 1 of the bundle branches due to the prolonged rapid rate, it is most likely to occur in individuals in whom there is heart disease.

The authors conclude that paroxysmal bundle-branch block (without a very short P-R interval) is, as a rule, a sign of serious heart disease, most often due to coronary sclerosis, but in some cases associated with rheumatic heart disease, diphtheria, and factors that cannot be ascertained clinically. Serial electrocardiograms taken during myocardial (congestive heart) failure, coronary insufficiency, and elevated heart rates may reveal transient defects in bundle-branch conduction.

Intraventricular Block in Acute Coronary Artery Occlusion

A. M. Master, S. Dack and H. L. Jaffe²² stress the fact that the sudden appearance of bundle-branch block may be the first electrocardiographic sign of acute coronary artery occlusion. In an analysis of 375 cases of acute coronary artery occlusion, intraventricular block, including bundle-branch block, evidenced by widening of the QRS interval to 0.12 second or more, was present in 57 cases (15 per cent). There were 48 males and 9 females, a ratio of 5.4:1, whereas the ratio for patients with normal conduction was 37:1. The average age of 59 years was slightly higher than that of 55 years for the patients without conduction defects. Defective intraventricular

conduction was usually associated with long-standing hypertension, cardiac enlargement and congestive heart failure, the respective incidence of each being 77, 84 and 92 per cent, which was definitely higher than in a large control series. When the QRS interval measured more than 0.15 second, cardiac enlargement and failure were practically universal. Repeated attacks of coronary occlusion may result in a progressive increase in the QRS duration. Intraventricular block often was associated with impaired auriculoventricular conduction; but other arrhythmias were not more common than in coronary artery occlusion in general.

The conduction defect generally was observed on the first day, and was usually permanent; in 6 patients it was transient. Specific symptoms or physical signs of bundle-branch block were not usually present; palpable reduplication of the apical impulses was observed only occasionally and splitting of the first heart sound in only 4 cases. Gallop rhythm was present in 60 per cent of the cases, but it was probably due to the associated severe heart failure. Left bundle-branch block of the common type, evidenced by left axis deviation and widening of the QRS interval to 0.12 second or more, occurred in 51 per cent of the 57 cases, typical or atypical right bundle-branch block in 28 per cent and intraventricular block in 21 per cent. The configuration of the ventricular complexes, as well as the axis deviation, often varied in serial records. In the presence of intraventricular block, characteristic electrocardiographic signs of myocardial infarction failed to appear in one-third of the cases. Nineteen cases presented the T_1 pattern associated with anterior wall infarction, and 9 the T_2 pattern of posterior infarction; in 10 there were changes in all 3 standard leads sug-

gesting both anterior and posterior infarction. The precordial lead may be of diagnostic importance, in that progressive S-T and T-wave changes may occur only in this lead. Absence or marked diminution in the initial positive deflection in this lead is usually due to anterior wall infarction even when bundle-branch block is present, although occasionally the latter alone is the cause.

Defective intraventricular conduction in coronary occlusion adds to the seriousness of the prognosis, the mortality rate being 42 per cent in comparison with 23 per cent in patients with normal conduction. Not only is the coronary artery sclerosis usually advanced, but at necropsy evidence of previous closures of 1 or more coronary arteries is almost universal. As a rule, the increase in mortality and the severe heart failure occurred in the cases with QRS interval of 0.14 second or more. Only occasionally was bundle-branch block present without evidence of cardiac failure or enlargement. Mortality rate and incidence of heart failure were not influenced by type of conduction defect, being the same whether left or right bundle-branch block or intraventricular block was present.

The anatomical basis for the conduction defect was septal infarction (which was present in four-fifths of the hearts). No correlation could be made between the vessels occluded or the location of the septal infarct and the type of conduction defect. Occlusion of the right coronary artery was as frequent as that of the left, and anterior infarction was as common as posterior infarction, regardless of the type of block. The persistence of normal conduction in many cases with septal infarction is attributed mainly to the presence of adequate collateral circulation in the septum. Transient bundle-branch block is probably due to anoxemia resulting from shock, tachy-

cardia and heart failure. The vagus nerve probably played no rôle in bundle-branch block, as no change was effected by the injection of atropine.

Treatment—The treatment of coronary artery occlusion with bundle-branch or marked intraventricular block is the same as that of coronary occlusion in general, with special attention to heart

intake, low caloric diet, *oxygen administration* and *mercurial diuretics* in conjunction with *acidifying salts*. *Oxygen therapy* is particularly beneficial for defective intraventricular conduction associated with tachycardia and heart failure. *Aminophyllin*, administered intravenously, has proved of especial benefit. The use of digitalis should

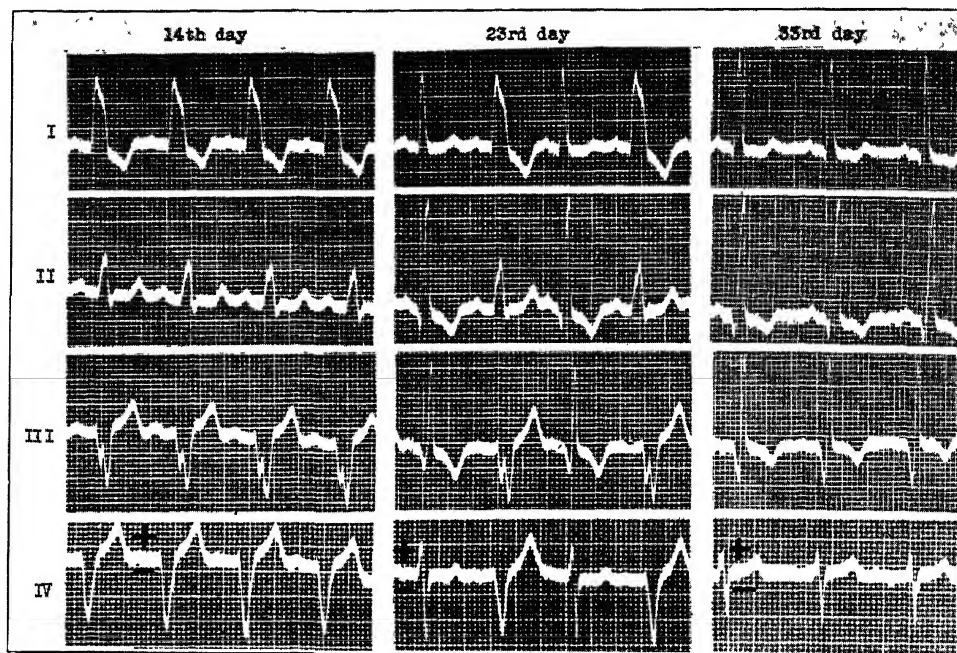


Fig 1—Case 7. Female, age 47 years. Transient and intermittent left bundle-branch block following acute coronary occlusion. The bundle-branch block is constant until the fourth week, then every alternate beat is conducted normally, resulting in 2:1 bundle-branch block. The latter disappears on the thirty-third day. The bundle-branch block masks the Q-T pattern of posterior infarction present in the normally conducted beats. The initial positive deflection is absent only when bundle-branch block is present. The patient recovered. (Courtesy, Am Heart Journal, Sept. 1938.)

failure. The regimen followed by Master and his coworkers^{23, 24} consists essentially of *complete physical and mental rest*—with sufficient sedatives and analgesics to control apprehension and pain, good nursing, and a *low caloric diet* (of approximately 800 calories) which eliminates gastrocardiac reflexes, lowers the basal metabolic rate and diminishes the work of the heart. Because of the high incidence of congestive failure, emphasis is placed on *diminished fluid*

be avoided in the early stages of coronary artery occlusion, as it may prove toxic in ordinary therapeutic doses; it should be administered only when other measures for the treatment of congestive failure have failed. *Quinidine sulfate* has been advocated in coronary occlusion to prevent ventricular tachycardia; but, in the presence of bundle-branch block or intraventricular block, it should be administered with caution because of the danger of increasing the conduction defect.

Lateral Infarction of Left Ventricle

The electrocardiographic signs of anterior apical and posterior basal myocardial infarctions have been well established for some years. Recently the electrocardiographic features of acute "lateral" or "midventricular" infarction have been found by F. C. Wood, C. C. Wolferth and S. Bellet²⁵ to consist of (a) a

cumflex branch of the left coronary artery²⁶ But, when this vessel carries an unusually large part of the myocardial blood supply, its obstruction may produce a more extensive lesion, invading the anterior or posterior wall of the left ventricle, with consequent complex electrocardiographic patterns. The electrocardiogram is a much less sensitive diag-

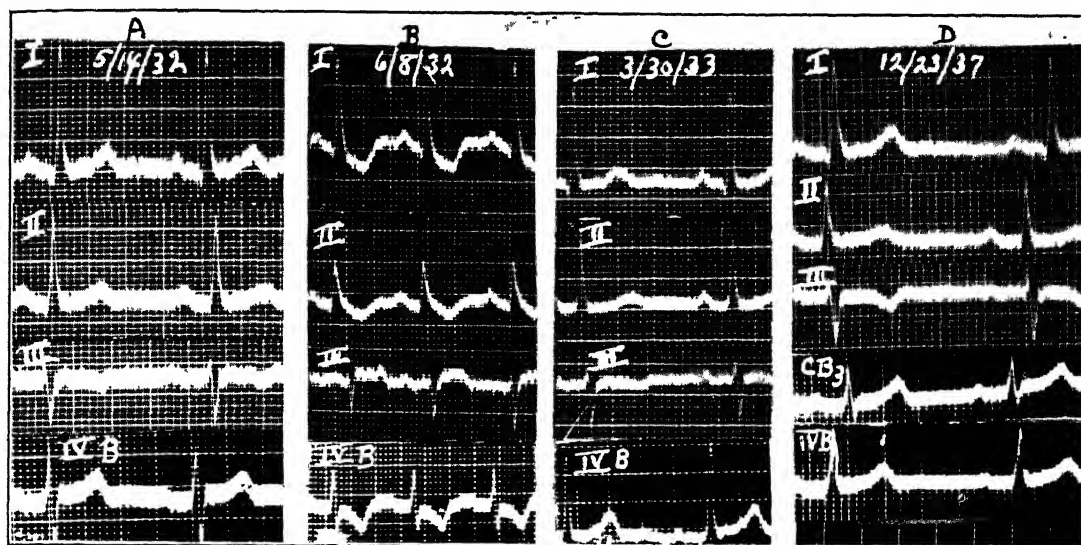


Fig 2—Electrocardiograms in case 7. *A* Tracing taken May 14, 1932, 3 weeks before the attack. It is normal except for left axis deviation. *B* Tracing taken June 8, 1932, 2 hours after the onset of the attack. The RS-T interval is depressed in Leads I, II, and IV. Lead III shows slight left axis deviation and a slight RS-T interval elevation. *C* Tracing taken March 30, 1933, 15 months after the attack. It is very much like the electrocardiogram of May 14, 1932, prior to the cardiac infarction except that the S-wave in Lead IV-B has disappeared. This did not take place immediately after the attack but at some time between June 20, 1932, and March 30, 1933. *D* Electrocardiogram taken Dec 23, 1937 showing that the S-wave in Lead IV-B is still absent. In a lead taken with the precordial electrode nearer the sternum (CB₃), the S-wave is present but much smaller than it was in Lead IV-B before the attack. (Lead CB₃ is ordinarily expected to have a larger S-wave than Lead IV-B.) (Courtesy, Am Heart Journal Oct 1938.)

depression of the RS-T interval in Lead IV, (b) a depression of the RS-T interval in Leads I and II (commonly, though not universally present), and (c) an absence of the signs of posterior infarction in Lead III (Fig 2). In the typical case, the RS-T interval depression in precordial leads is more marked when the anterior electrode is placed at or to the left of the apex than when it is near the sternum.

Midventricular or lateral infarction usually results from occlusion of the cir-

cumflex branch of the left coronary artery. Even when several precordial leads are used, a lesion in the left lateral wall, though incompletely healed, can escape recognition.

The electrocardiographic pattern of acute "lateral" infarction can be simulated rather closely by digitalis action. However, comparatively few patients have marked RS-T interval deviations from digitalis without toxic symptoms, such as nausea and vomiting, or marked

asthenia; and few digitalized patients show the exact pattern of lateral infarction. The electrocardiographic features of the acute lesion may subside very rapidly, and during the process of healing the tracing may be indistinguishable from that of certain hypertensive patients without myocardial infarction. After healing of the infarction, all the changes may disappear from the tracing

entiated because it has a significant Q_3 ; and an elevation of the RS-T interval in Leads II and III; and pulmonary embolism differs in that T_1 is usually upright and T_3 usually inverted.

Effect of Tobacco on Electrocardiogram

Observations of the effect of the inhalation of tobacco smoke on the electrocar-

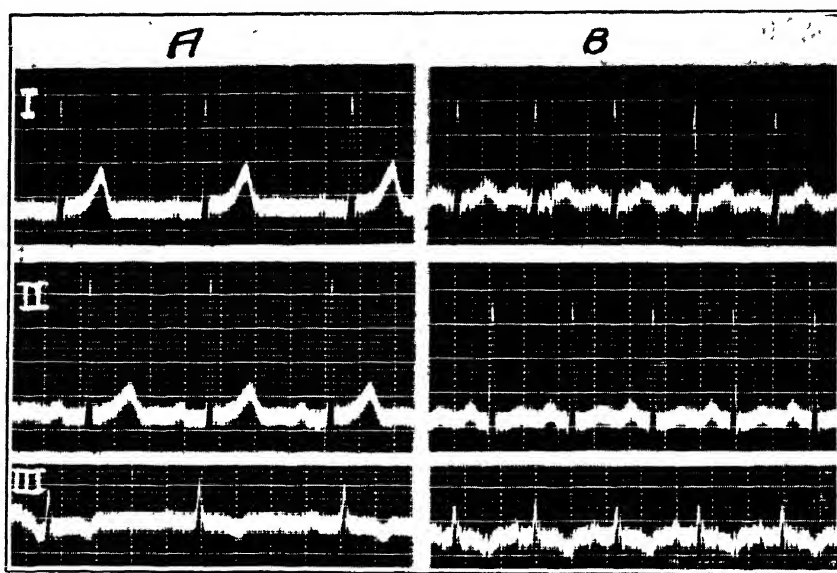


Fig. 3—Electrocardiograms from a healthy woman aged 26 years. *A* Control, heart rate 80, blood pressure 110/75. *B* After smoking, heart rate 130, blood pressure 120/90. (Courtesy, *Am Heart Journal* Jan, 1938.)

For some unknown reason there is a high incidence of auricular fibrillation in lateral infarction. Without knowledge of these facts, there is danger of overlooking the presence of this type of acute infarction.

The electrocardiographic pattern can be reproduced also by the temporary ischemia of effort angina, in that the QRS complex usually is unaffected. Furthermore, it might be confused with posterior infarction on the one hand, or with pulmonary embolism on the other, in that the precordial leads of the 3 conditions may be similar. However, posterior infarction can usually be differ-

entiated because it has a significant Q_3 ; and an elevation of the RS-T interval in Leads II and III; and pulmonary embolism differs in that T_1 is usually upright and T_3 usually inverted. The individual to be tested was requested not to smoke for at least 1 hour preceding the test; a control electrocardiogram was taken, after resting comfortably in a chair or bed until the blood pressure and pulse rate attained steady values; and then the smoke of the cigarette was inhaled until either toxic symptoms appeared or the cigarette was finished.

Thirty-nine of the 45 patients showed on smoking an increase in heart rate which averaged 13 a minute; 24 of 31

individuals tested showed an increase in arterial blood pressure, averaging 13 mm. of mercury systolic and 7 mm. diastolic. Twenty of the 45 showed on smoking significant electrocardiographic changes other than variation in heart rate. Of the 20, 2 were nonsmokers, 1 smoked occasionally, and 17 were heavy smokers; 10 gave a history of symptoms on smoking, and 15 had symptoms while the test was being done. The commonest electrocardiographic finding, a decrease of from 1 to 4.5 mm. in amplitude of the T-waves in Lead I or II, was observed in 15 instances (Fig. 2). In 2 instances there was an increase in the amplitude of T in Lead I or II.

The probable explanation of the T-wave changes lies in the characteristic action of nicotine on the cardiac ganglia. Approximately 20 mg of nicotine is taken into the circulation on smoking a cigarette, which amount is sufficient to produce its characteristic action, *viz.*, stimulation of the entire nervous system followed by depression. In a susceptible individual, the initial lowering of the T-waves occurs during the inhalation of the tobacco smoke, but the maximum lowering or even inversion of T occurs shortly after smoking ends. The inversion or flattening of T lasts only a few minutes, and within half an hour the waves assume their normal form and amplitude. If a second cigarette is smoked while the waves are still flattened as a result of the first, they may temporarily increase in amplitude, due presumably to sympathetic stimulation. This increase in amplitude is quickly followed by a decrease and the waves may become lower than before.

The T-wave changes after smoking were found to be similar to those following full atropinization. The individuals showing marked lowering or inversion of the T-waves with tobacco and with

atropine were young and healthy but emotionally labile; more stolid individuals, even those with severe coronary sclerosis, did not show these T changes. The cardiac effects of the small amounts of nicotine absorbed during smoking appear to be due to parasympathetic paralysis and sympathetic stimulation. In individuals with small coronary reserve and unusual sensitivity to tobacco smoke, in whom attacks of angina pectoris are precipitated by smoking ("tobacco angina"), the attacks are not the result of coronary vasoconstriction, but the result of a sudden increase in the work of the heart, as shown by the increase in blood pressure, or heart rate, or both.

EFFECT OF INTRAVENOUS FLUIDS ON CARDIOVASCULAR SYSTEM

In recent years the injection of fluids intravenously to combat dehydration, maintain nutrition, and to treat shock has increased considerably. Although the benefits from this procedure are generally striking, untoward effects may occur under certain circumstances. The effects of fluids injected intravenously on the hematocrit, concentration of plasma protein, and blood volume have been studied by D. R. Gilligan, M. D. Altschule, and M. C. Volk²⁸ in 34 patients not suffering from shock, most of whom showed no evidences of dehydration or cardiac or renal insufficiency. Many of the patients were surgical cases who had had appendectomies, herniorrhaphies, or pelvic repairs; intravenous fluids were administered 3 to 6 hours postoperatively. The fluids injected were 0.85 per cent saline, 5 per cent glucose, or 5 per cent glucose in physiological saline solution. The hematocrit and the concentration of serum protein were always found lower after the injection of

from 450 to 1500 cc. of fluid. Plasma and blood volume changes were estimated by (a) calculation from the control blood volume and the protein and hematocrit findings before and after injection, (b) directly by the "Evans Blue" dye method, and (c) by calculations from the control blood volume and hematocrit findings alone. Plasma and blood volumes were found increased immediately after the end of injection. In individuals receiving a given volume of solution of given composition, the greatest increases in blood volume usually were obtained after the faster rates of injection, and the lesser increases at the slower rates of injection. The average increases in plasma and blood volumes were somewhat greater when the hypertonic solution of 5 per cent glucose in physiological saline was given than after plain physiological saline solution.

The percentage of the injected fluid present in the circulation decreased after the volume of fluid injected increased. The results indicate that after intravenous fluids the forces which govern the escape of fluid from the circulation normally act to resist increases in blood volume of over approximately 20 per cent. The plasma and blood volumes were found appreciably increased up to approximately 2 hours after injection of 1000 cc. of 0.85 per cent saline or of 5 per cent glucose in 0.85 per cent saline at rates of 30 cc. per minute or greater. It was found that operations of the order of uncomplicated appendectomies or inguinal herniorrhaphies do not cause appreciable reduction in blood volume, as evidenced by the absence of change in hematocrit and concentration of serum protein after operation; and that the increase in blood volume after injection of fluids intravenously is not influenced by such operations.

In a subsequent article, the effects on the *cardiovascular dynamics* of a rapid increase in blood volume, occurring as a result of the intravenous injection of 500 to 1500 cc. of physiological saline, 5 per cent glucose or 5 per cent glucose in physiological saline solutions at rates of less than 20 cc. per minute, have been reported by M. D. Altschule and D. R. Gilligan.²⁹ Very slight changes were observed in the cardiovascular functions studied, even though the blood volume was usually considerably increased. When these volumes of fluid were injected at more rapid rates, considerable increases in venous pressure, cardiac output, velocity of blood flow, and in blood volume usually were observed; and increases in pulse rate, pulse pressure, and in the P-wave of the electrocardiogram were observed in some instances. The greater venous pressure increases occurred in individuals who received fluids at the larger volumes and at the more rapid rates. The venous pressure invariably returned to the control level within 10 to 25 minutes after the end of fluid administration. Significant increases in cardiac output occurred in patients in whom the intravenous injection of fluids resulted in rises in venous pressure.

When fluids were injected in larger volume and at more rapid rates, the increase in velocity of blood flow was considerably less than that expected from the changes in cardiac output. In some instances the increase in velocity of blood flow was greater after the injection of 500 cc. of fluid than after 1000 or 1500 cc. These findings have been interpreted as indicating an increase in pulmonary blood volume during injection. Dyspnea did not occur and changes in respiratory dynamics were not observed. In general, somewhat greater changes in the cardiovascular dynamics were observed during injection of the solution containing 5

per cent glucose in physiological saline than when the isotonic solutions, plain physiological saline, or 5 per cent glucose in distilled water, were injected. (An increase in blood volume of approximately 200 cc. during the first few minutes after the injection of 50 cc. of 50 per cent glucose in saline has been demonstrated by J. G. Gibson, 2nd, and W. A. Evans, Jr.³⁰

The fact that rises in venous pressure did not persist, or even did not occur, in spite of increased blood volume, together with the observation of increasing diffuse flush of the skin, suggest a progressive peripheral vasodilatation during the course of injection of fluids. Additional evidence in this regard is the tendency toward increased pulse pressure observed in some subjects.

Intravenous infusions which continue for a period of several days impose conditions favoring the development of edema, both peripheral and pulmonary, even though in such cases the fluid is given at very slow rates. The lowering of the plasma protein level due to plasma dilution, vasodilatation due to increased blood volume, and the tendency toward increased venous pressure by operating together over a period of days, may result in clinically perceptible edema.³¹

The results of these studies suggest that when it is necessary to administer fluids intravenously to elderly debilitated or cardiac patients, the fluid should be isotonic, in small volume, and injected slowly, *i. e.*, at rates of 15 cc. per minute, in order to avoid the danger of pulmonary edema and of angina pectoris, which might be occasioned by the increased cardiac work. An additional factor favoring the development of pulmonary edema is the increase in the volume of blood in the lungs occurring during the intravenous administration of large volumes of fluid. In the treatment

of incipient shock, however, when blood transfusion is not immediately available, the crystalloid solution to be given intravenously should be hypertonic, in large volume, and injected rapidly, *i. e.*, at rates over 30 cc. per minute.

METRAZOL IN COMPLETE HEART BLOCK

Four cases of complete heart block and Adams-Stokes syndrome, treated with *metrazol* (pentamethylenetetrazol), of whom 2 were greatly benefited by the drug and 2 were not, have been reported by H. C. Lueth.³² Although *cardiazol*, as *metrazol* is called in Europe, frequently has been reported as a successful remedy for circulatory collapse, careful animal experiments have failed to demonstrate any direct action on the heart.³³ A probable explanation of the beneficial effect of *metrazol* in complete heart block with the Adams-Stokes syndrome is that it stimulates the vasomotor tone and respiration. Lueth believes that *metrazol* compares favorably with any of the other drugs now in use, *viz.*, atropine sulfate, barium chloride, epinephrine and ephedrine. *Metrazol* possesses an advantage, in that it may be used for prolonged periods with no apparent untoward side effects.

PERIPHERAL CIRCULATORY DISEASE

Evaluation of Results in Treatment

The need of consideration of various factors in the evaluation of the great variety of methods of treatment of peripheral vascular disease which have been proposed during the past decade (Table 3) is stressed by S. Silbert.³⁴ There must be kept in mind the spontaneous improvement occurring after arterial occlusion, the effect of cessation of

TABLE 3
METHODS USED IN TREATMENT OF PERIPHERAL
VASCULAR DISEASE

Physiotherapy measures

Heat

Hot baths

Baking

Thermo-regulated cradle

Diathermy

Short wave

Whirlpool baths

Buerger's exercises

X-ray treatment over spine

Suction-pressure apparatus (Pavaex)

Intermittent venous hyperemia

Injections

Hypertonic sodium chloride

Sodium citrate

Typhoid vaccine

Insulin-free pancreatic tissue extract

Paravertebral injections of alcohol

Subarachnoid injections of alcohol

Sodium thiosulfate

Drugs

Acetylcholine

Theobromine

Mecholin

Nitrites

Iodides

Papaverine

Alcohol

Allantoin

Thioglycerol

Operations

Perivascular sympathectomy (Leriche)

Ganglionectomy

Arteriotomy

Vein ligation

Peripheral nerve section

(Courtesy Am Heart Journal Mar 1938)

smoking, and the normal variation in vasoconstriction due to environmental changes in temperature and in the patient's psychic state

After occlusion of a major artery, *collateral circulation develops quickly, spontaneously*, for about a year and continues to do so at a slower rate for at least another 2 or 3 years. Following this first period the circulation remains at a remarkably stationary level for an

indefinite number of years, during which the collateral circulation is maintained. In patients with arteriosclerosis there follows a third period in which the collateral circulation itself becomes involved in the arteriosclerotic process, and a progressive diminution of circulation results. In the first period, treatment may accelerate the development of the collateral circulation, although it will develop without it. Therefore, in order to evaluate therapy properly, it is necessary to know the exact stage of the disease process

Clinical experience has demonstrated that *cessation of the use of tobacco* in itself results in a definite improvement in circulation. The constant use of tobacco apparently maintains the vessels in a greater degree of vasoconstriction than normal. In 20 cases of thromboangitis obliterans observed by Silbert, in which the disease was in a relatively early stage, cessation of smoking without any other form of therapy resulted in improvement or disappearance of all symptoms

Changes in environmental temperature must receive proper consideration in the interpretation of circulatory measurements by means of the oscillometer, and of skin temperature readings by means of electric thermometers. In a cold room, with the vessels constricted, the oscillometer reading at the ankle, which is normally between 4 and 5, may be reduced to 3 or less, in a hot room the reading may be as much as 6. Similarly, in a cold room the surface temperatures of the great toe may be 68° F (20° C) and in a hot room 93° F (34° C). The degree of vasoconstriction in peripheral vessels is influenced also by the *mental state of the patient*, increased nervousness or emotional disturbance being likely to produce constriction

Even with advanced organic disease of the peripheral vessels, there is still

some *superimposed vasoconstriction* reducing the amount of blood flow to the extremity. It is only in the last stages of peripheral vascular disease, when the integrity of the extremity is actually threatened by loss of blood supply, that this ability to vary the volume of peripheral circulation is lost. The degree of superimposed vasoconstriction can be determined by the use of any form of anesthesia. The simplest method consists of a novacaine injection of the posterior tibial nerve in the ankle, which procedure releases whatever vasoconstriction might be present in the vessels of the foot, causing an elevation of temperature which attains its maximum in about 15 or 20 minutes. The oscillometer measurement then taken at the ankle reflects the maximum dilatation possible in a diseased vessel. A comparison made under similar conditions 6 months later will be convincing evidence of any circulatory improvement.

All the patients attending circulatory clinics are not suitable for evaluating the results of treatment. "The ideal case is an individual who has had intermittent claudication for at least 2 to 3 years or so that the phase of spontaneous improvement has passed, one who has stopped smoking for more than a year, and perhaps one who has been treated for a considerable period by some method without improvement. This will rule out any psychic factor due to contact with the physician and will show that spontaneous improvement is not taking place. The circulation in such a patient should be studied by means of oscillometer readings and temperature studies after complete vasodilatation has been produced under anesthesia. He is now ready to be treated. If during the next year he shows steady subjective improvement and this improvement is supported by objective evidences, such as increased

oscillometer and temperature readings under controlled conditions, we may permit ourselves to accept such evidence as indicating the value of the treatment."

The Outlook in Thromboangiitis Obliterans

A study of 948 cases of thromboangiitis obliterans, observed at the Mayo Clinic from 1907 to 1937, inclusive, has been made by B. T. Horton.³⁵ Patients came from every state in the Union except 3, and from 10 foreign countries; more than 28 different nationalities were represented. Two hundred and sixty-two (28 per cent) of the patients were Jews; 686 were Gentiles. In all cases the same fundamental pathologic process was present, and the signs and symptoms, as well as the clinical course of the disease, were strikingly similar. Twenty-one of the patients were women. The mean age of the male patients was 41.8 years; of the women, 38.8 years. Eight hundred and eighty (93 per cent) of the patients were cigarette smokers.

Of the 262 Jewish patients, 88 (33.6 per cent) underwent amputation, and of the 686 Gentile patients, 313 (45.6 per cent) underwent amputation. Bilateral amputation of the legs was performed in 85 cases, 16 of the individuals were Jews, and the remaining 69 were Gentiles. Approximately 70 per cent of the patients went for a period of 3 years from the onset of the disease without the necessity of amputation, while only 60 per cent went for a period of 5 years, and only 40 per cent for a period of 10 years without amputation.

Apparently the most important factors which determine whether an individual who has thromboangiitis obliterans will continue to walk on 2 feet throughout life are *early diagnosis* and *education of the patient concerning the nature of the disease and the care of his extremities*.

The most frequent errors in diagnosis consist in mistaking claudication in the foot for arthritis or fallen arches, and the abnormal rubor of the toes for infection. In the presence of symptoms referable to the hands, feet, or legs, the essential point to establish is whether the complaint is attributable to disease of the vessels and, if it is, whether the disease is occlusive or vasomotor.

Patients must be cautioned to **avoid trauma and undue exposure to cold**. The slightest abrasion should be carefully treated and regarded as if it were a major injury. **Soft woolen stockings** always should be worn in cold weather. The feet should be **washed carefully** and **dried gently** with a soft towel. The occasional application to the feet and toes of a **50 per cent solution of alcohol** is desirable, but this should not be used to excess. If the feet are excessively dry or if the skin tends to crack or undergo scaling, **hydrous wool fat** or **theobroma oil** can be rubbed in gently to soften the skin. In numerous cases gangrene has been caused by the use of strong disinfectants, chemical compounds, ointments, corn cures, and remedies for athlete's foot. A safe method for treating athlete's foot is to soak the feet for a half hour each day in 1:8000 solution of **potassium permanganate**, which should be made up fresh for each soaking. Toenails should be cut straight across, after being soaked in warm water, and they should be scrupulously but carefully cleaned. Corns, callouses, and bunions should not be cut. Removal of ingrown toenails and minor operations on the toes should be performed only by a surgeon familiar with the problems involved in occlusive arterial disease. When injury to the toes and feet does occur, absolute rest in bed is indicated. In many cases in which gangrene has developed and amputation

has been necessary, such a calamity might have been avoided if proper precautions had been taken sufficiently early.

Effect of Iontophoresis with Acetyl-Beta-Methylcholine Chloride on Peripheral Blood Flow

Iontophoresis with 0.2 per cent acetyl-beta-methylcholine chloride contained in a plethysmograph has been found by H. Montgomery, H. E. Holling, and C. K. Friedland³⁶ to cause invariably a marked increase in blood flow in the treated hands of 6 healthy young adults and 3 young male patients with thromboangiitis obliterans and definite occlusive disease of the arteries of the hands. The latter patients had more severe obliterative changes in the feet, but in each case there were sufficient changes in the hands to produce cold, blue fingers, decreased oscillations at the wrist, and a delayed filling of the hand as determined by an Allen test. The experiments were carried out in a room maintained at constant temperature by automatic control. The source of current for iontophoresis consisted of a 45-volt "B" battery, and was controlled by a 10,000-ohm variable resistance. A 60-milliampere fuse was kept in the circuit. Current was turned on at about 4 ma., and gradually increased or decreased at a rate consistent with the comfort of the patient. Currents of 20 to 35 ma. were used for periods of 35 to 90 minutes. As the plethysmograph was made of metal, it was possible to utilize it as a positive electrode. The negative electrode, consisting of a sheet of copper screening 10x14 inches covered with several layers of gauze and one of light canvas, was moistened with saline and applied to the back of the thorax.

As a rule, the effect began after the current had been on for less than 15 minutes, reached a maximum within

about 30 minutes, remained at that point as long as the current continued to flow, and began to decline almost as soon as the iontophoresis ceased. The duration of the increasing blood flow after the current was turned off varied considerably, but usually recovery was practically complete within an hour (the shortest duration being 30 minutes, the longest more than 105 minutes). The patients with diseased arteries responded in the same general way as the normal subjects, although increase in blood flow was somewhat less marked. In the normal subjects the initial flows varied between 1 and 14 cc. (average 4 cc per minute per 100 cc of hand), and between 12 and 32 cc. at the height of the acetyl-beta-methylcholine chloride effect. In patients with obliterative disease, the initial flows varied between 1 and 14 cc., those at the height of the drug's effect being 12 and 24 cc. No increase in blood flow was ever observed in the untreated (control) hand. Current without the drug produced either a slight rise or no rise in blood flow through the control hand. The drug without current had no effect on blood flow. No conspicuous signs of systemic effects were observed. In several instances there was a slight increase in intestinal peristalsis, and in one there was a slight fall in systolic blood pressure, pulse rate was not significantly affected. The treated hand sometimes showed slight reddening, and occasionally there was sweating of this hand for 1 or 2 hours after the treatment. The prolonged exposure to the fluid in the plethysmograph usually produced thickening, corrugation, and whitening of the skin, but neither hyperemia nor sweating could be detected. However, a pounding sensation occurred in the hand at the height of the reaction. In 1 case there was mild tanning of the

skin area exposed to iontophoresis, lasting several days; but no burns resulted.

These results confirm the belief that iontophoresis with acetyl-beta-methylcholine chloride produces marked dilation of the blood vessels in the treated part. The effect seems to be too great to be attributed to changes in the most superficial vessels alone; it is probably exerted upon deeper vessels as well. In 2 subjects acetyl-beta-methylcholine chloride iontophoresis increased peripheral blood flow to about the same extent as would reflex vasodilatation produced by application of heat to the legs. The therapeutic possibilities of reflex vasodilatation have not been tested.

In a series of 20 experiments on dogs anesthetized with chloralose and ether, systemic rather than local effects of the drug predominated. It is not known whether this result is a species difference or is related to experimental conditions. The systemic effect varies with the concentration of the drug and the strength of the current, but is independent of the size of the electrode within the range of sizes used. Mild, generalized increase in peripheral blood flow usually was occasioned.

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DERMATOLOGY

By JOHN B LUDY, M D

NICOTINIC ACID¹

Reaction to Its Oral Administration- The treatment of pellagra with nicotinic acid often produces a sensation of heat and tingling of the skin. These sensations often appear within 10 minutes, last from 10 to 20 minutes and are accompanied by dilatation of the peripheral blood vessels with a slight temporary fall in blood pressure.

Some clinicians report a marked flushing of the face, neck, chest and arms a few minutes after intramuscular injection of 60 mg of nicotinic acid, which lasts about 15 minutes. A similar reaction followed intravenous administration of approximately 12 mg. These observers found that the pulse, respiration and blood pressure were not affected and that there was no discomfort except for a slight feeling of warmth.

The authors determined the quantity of nicotinic acid which may be given

by mouth to healthy subjects without producing these unpleasant reactions which tend to make continued treatment with the drug more difficult. Accordingly a group of 18 healthy adult women were given an identical diet containing approximately 2400 calories and low in the pellagra-preventive vitamin. Six were given 50 mg, 6 were given 30 mg and 6 were given 10 mg of nicotinic acid daily in aqueous solution added to 4 ounces (120 cc) of tomato juice and taken with the midday meal. The experiment was continued for 92 days and their conclusions are that nicotinic acid in daily doses of 50 mg, given orally produced transient, unpleasant but harmless reactions in 4 of 6 adult women on a diet restricted in the pellagra-preventive factor. A daily dose of 30 mg of nicotinic acid produced a similar reaction in 2 of 6 women. Therefore reactions are to be expected in some persons on

continued treatment with nicotinic acid in daily doses as low as 30 mg. orally.

Although the reactions are disagreeable, they persist only a short while and there is no evidence that any harm is done by them. Therefore, their occurrence should not be allowed to interfere with the therapeutic use of large doses of nicotinic acid.

ACUTE SEBORRHEIC DERMATITIS OF EXTERNAL EAR

G. Scharff² states that acute seborrheic dermatitis of the external ear is practically always secondary to seborrhea of the scalp. The patient usually complains of pain in and around the ear which manifests itching and deafness. Examination of the meatus reveals swelling, erythema and scale formation with the presence of an occasional watery discharge. The condition often spreads to the auricle which is characterized by edema and the formation of small vesicles.

Treatment of the scalp and middle ear pathology, when present, is of primary importance. A 2 per cent solution of *salicylic acid* is applied to the scalp and frequent *tar shampoos* are employed.

The meatus is best treated by instillation of a mild antiseptic oil such as

R *Ung. hydrarg. oxid. rub.* 3j (40 Gm.)
Oil cinnamon m℥ (0.05 cc.)
Oil amygdalae dil. f℥j (30 cc.)

Sig. Instil in external auditory meatus twice daily.

When extensive exudation is present a powder such as *calamine* or *zinc oxide* should be insufflated. Whenever debris is present in the meatus syringing with *warm boric acid solution* is indicated and beneficial. Treatment should be continued for several months.

Chronic seborrheic dermatitis may follow the acute form and may be of 2

varieties: (a) Dry and scaly type; and (b) sclerotic form. The dry and scaly type of chronic seborrheic dermatitis usually is caused by a staphylococcal infection. Its treatment is the same as for the acute form. The sclerotic type of seborrheic dermatitis is invariably due to a secondary streptococcal infection. The patient may be deaf and complains of intermittent pain and itching. Deafness results from the accumulation of debris which blocks the auditory canal. The meatus is red and considerably thickened. This may result in the formation of fissures.

Treatment consists of the instillation of an alcoholic solution of *flavini*, 1 : 2000. If the auricle is involved a *tar* or an *ichthyol ointment* should be employed.

TREATMENT OF DERMATITIS CAUSED BY OILS

Turners, polishers and all workers who get in contact with grease and oil are particularly liable to a form of dermatitis which usually involves the hands and forearms. The lower extremities and abdomen, owing to contact with clothing impregnated with oils and grease, also may be the seat of a dermatitis.

Methods for treatment and prevention of this condition are given by A. Feil.³

The obstruction or occlusion of the sebaceous glands and their ducts by the oil and grease leads to the formation of acne-like papules and boils. Treatment consists of a thorough *washing* of the affected areas with *soap and warm water*. This softens the epidermis and removes the comedones from the follicles. The following ointment should be applied frequently.

R *Sulfur precipitate* 5j¼ (5 cc.)
Pulv. talc venet. 3½ (2 cc.)
Glycerin f℥j (60 cc.)
Tincture quillae 5j¼ (10 cc.)
Aqua Rosae f℥iv (120 cc.)

Prophylactic measures include the wearing of rubber gloves and mackintosh overalls. Periodic cleansing of the machinery and sterilization of the oils is essential and protective.

LEUKOPLAKIA BUCCALIS

Dr F J Eichenlaub⁴ investigated 327 cases of leukoplakia occurring among 16,802 (19 per cent) veterans of the World War. The average age of this group was about 40. They were all males and less than 5 per cent were negroes.

A careful study was made of every patient which included a complete physical examination. A routine Wassermann test was made for every patient. Leukoplakia has long been recognized as a possible soil for the development of carcinoma in the oral cavity. Among the 16,802 veterans examined, carcinoma of the oral cavity was encountered on the lips in 19 cases, on the cheek in 1, and in the larynx in 6. In only 4 of these, 3 in which the lip and 1 in which the buccal mucosa were involved, was the carcinoma directly associated with leukoplakia. Of the 6 cases with carcinoma of the larynx 4 had leukoplakia of the mouth, but the records failed to show whether there was any leukoplakia in the larynx.

Eichenlaub submits the following summary:

Among 16,802 patients examined, 327, or 19 per cent, had leukoplakia buccalis.

Tobacco was used by all but 5 of the 327 patients.

Syphilis was 3 times as common among the patients with leukoplakia as it was among the whole group. Nevertheless, syphilis could be entirely excluded in over 80 per cent of the cases. I do not believe, therefore, that syphilis is an important factor in the etiology of leukoplakia.

Infections of the mouth, the ears, the nose, the throat, the respiratory tract and other common sites of infection were somewhat more prevalent among patients with leukoplakia, but there was not enough difference to attribute any etiologic importance to these factors.

Of 327 cases of leukoplakia, carcinoma involved the lip in 1, the cheek in 1 and the larynx in 6. In only 4 of these, however, was carcinoma directly associated with the lesion of leukoplakia.

It is probable that leukoplakia is the result of an inherent tendency to hyperkeratosis following local irritation, and not of any constitutional disease.

TREATMENT OF PSORIASIS WITH ETHYL CHLORIDE⁵

Ethyl chloride was first employed in combination with *mercury quartz irradiation* in a series of patients suffering from psoriasis. The ethyl chloride is sprayed on the psoriatic patch until slight freezing occurs and the patient complains of a burning sensation. This is repeated daily or at 2-day intervals until the patch disappears.

The author noted that while the larger areas of psoriasis were treated the smaller ones also involuted. This would seem that apart from the local action of ethyl chloride it appears to exercise an activating influence on the blood stream which is also beneficial to untreated areas.

Dr Ford Anderson⁶ of Washington, D C., reports a case of fulminating acute lupus erythematosus cured by *sulfanilamide*.

The patient, a white female age 28, was a native of Georgia and gave a history of having had discoid lupus erythematosus 6 years prior to the present attack of fulminating acute lupus erythematosus.

Apparently this attack followed the use of sodium gold thiosulfate. A few days after the last intravenous injection of sodium gold thiosulfate the patient developed a severe headache, articular and abdominal pains and a temperature of 103.5°F . (39.8°C .). All former local symptoms became more pronounced and assumed a dusky cyanotic hue. In addition erythematous lesions of varying size appeared on the face, shoulder, chest, arms and legs. The symptoms increased in severity and 3 or 4 days after the appearance of the fulminating disseminated type of lupus erythematosus the temperature was 105°F (40.5°C .) associated with extreme prostration and the patient was then removed to the hospital.

Patient was then given 15 grains (0.97 Gm.) of sulfanilamide by mouth and this dose was repeated every 4 hours until 60 grains (3.88 Gm.) were given. After this the patient was given 10 grams (0.65 Gm.) every 4 hours until a total of 40 grams (1.94 Gm.) was given. In 24 hours the temperature had fallen to 98°F (36.7°C .) It did not rise above normal during convalescence.

The dermatitis and constitutional symptoms began to disappear within 1 hour after the first dose of sulfanilamide. Three days after she had entered the hospital she was entirely free of symptoms and was discharged. Twenty-two days after leaving the hospital she was again interviewed and it was found that not only had the pigmentation disappeared but there was not the least sign of reaction at the sites of the old discoid lupus erythematosus.

ECZEMA IN INFANTS AND IN CHILDREN

Contact and Environmental Allergens as a Cause—E. D. Osborne, M.D. and H. L. Walker⁷ followed a definite

procedure in treating eczema in infants and children which has been regarded as most satisfactory. It consists of:

1 Investigation of:

(a) The family history of allergy. This is of slight importance in the individual case.

(b) A history of definite reactions to specific foods. This information is recorded for future use.

(c) The age at onset. We have never seen an infant under 10 days of age with eczema due to hypersensitivity.

(d) The exact location of the first area of eczema and the site of subsequent attacks, especially the first area to show evidences of exacerbation.

(e) Contact substances, including soaps, laundry chemicals, medicated oils, powders, wool, silk, feathers, dogs, cats, insect sprays, kapoc, the mother's and father's cosmetics, hand lotions and toys.

(f) Previous treatment, especially by local applications.

2 Examination of the patient, with particular attention to the area of onset, of sharply limited free areas, such as the nose, the upper lip and the chin and of sharp limitations at the ankles, the wrists and the cheeks. Evidence of dissemination of the offending allergen through the blood stream, and an estimate of the degree and extent of sensitization are extremely important.

3 Outline of treatment to the parents. This is often difficult because many intelligent as well as ignorant parents refuse to believe in the importance of external contact and environmental allergens. It is essential to convince them that the first procedure is the elimination of these factors, which requires from 4 to 8 weeks of observation. A list of the common contact and environmental allergens is given to them, with a detailed explanation that an infant must be kept in its crib or suspended in a canvas hammock and isolated from all contact and environmental allergens. We insist on the removal of all wool and silk from

the room, including carpets, rugs and blankets, followed by frequent use of a vacuum cleaner. In cases of severe eczema we have insisted on hospitalization, and in a number of instances the use of an air-conditioned room has been of great assistance. However, in our experience the ordinary children's ward, free of all of the common contacts, has proved adequate for a fair trial with all except highly sensitized children. One of the main benefits of the air-conditioned room is the maintenance of an absolutely even temperature and humidity. As is well known, a high temperature frequently leads to excessive scratching, and when the humidity is low the dryness of the skin tends to induce excoriation. We emphasize again that from 4 to 8 weeks is essential for a proper test in many cases. Hospitalization for such a period is impossible for many families unless free ward beds are at the disposal of the physician. Our best results have come in cases in which such accommodations have been available. When one is once convinced of the importance of contact and environmental allergens in a given case, any subsequent exacerbation should be investigated preferably by personal inspection of environment.

4. Subsequent office visits at 1- and 2-week intervals. Answers to well-directed, searching questions relative to all common eczema-producing contact and environmental substances should be elicited.

5. Application of plain *petrolatum*, *petrolatum with 0.5 per cent phenol* or equal parts of *olive oil and solution of calcium hydroxide*. These are the only medicaments indicated during the test period.

6. Search for the specific cause of the eczema when the child is free of eruption. This can be done by patch tests, which are not always conclusive and, in

our opinion, not as valuable as actual clinical trial.

7. Re-examination of the child and of the environment at the first sign of a recurrence.

8. Other methods of investigation, including elimination diets.

Investigation of contact and environmental allergens in eczema of infants and children brings a high percentage of satisfactory results.

There is no experimental evidence that a person inherits any specific epidermal sensitivity. He does inherit an "ease of sensitization" or a "susceptibility to sensitization."

The widespread use of ammoniated mercury in the prophylaxis of impetigo contagiosa in the newborn is an important factor in producing eczema of infants and in widening the base of their allergy.

In our opinion, routine scratch and intradermal tests are entirely inadequate, unreliable and misleading in investigations of eczema of infants and children.

Routine patch tests of infants and children are not usually satisfactory. Actual clinical trial is more important. Patch tests with protein substances generally produce negative results in infants and children. As widely used, they do not conform to the first rule of patch testing, namely that actual clinical conditions must be duplicated.

In an etiologic study of eczema of infants and children, we believe the first attack should be on the elimination of contact and environmental allergens. By this method we have succeeded in obtaining the following results: Fifty per cent were cured; 35 per cent were improved and 15 per cent were unimproved. In the "improved" group, we believe there were multiple sensitivities not only to contact and environmental allergens but to food atopens and possibly to metabolic products. From our experi-

ence, we do not believe that food atopens are of importance in more than 15 or 20 per cent of cases of eczema in infants and children.

Transepidermal absorption of water-soluble protein allergens through both inflamed and uninflamed skin explains many of the clinical facts observed in patients sensitized to these allergens.

A careful, painstaking investigation of the history, a highly developed detective instinct and infinite attention to detail are more important than routine tests

of any kind in determining the cause of eczema in infants and children.

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DIETOTHERAPY

By DEACONESS MAUDE BEHRMAN, B.S., and MIRIAM ADAMS, B.S.

Introduction—For the past few years we have been noticing that the trend in diet therapy has been away from specialization and a return to the normal well-balanced diet. Every dietitian is aware of the fact. After reviewing many articles on treatment of various diseases with diet, we only come to the end of the article to find the author saying, we must keep the patient well nourished with a well-balanced diet. When a diet is prescribed for a patient one of our first duties is to determine its adequacy, and then make an attempt to take care of inadequacies if there are any.

The following summary of an adequate diet is given for the benefit of those desiring to check diets for adequacy. It is taken from Food in Health and Disease by Katherine Mitchell.¹

In general, the requirements of an adequate diet are

AN ADEQUATE DIET

I Adequate Protein

1 For an adult

- 1 Minimum 0.65 Gm. of protein per kg. of optimum body weight

- 2 Optimum 1 Gm. of protein per kg. of optimum body weight

B For a child

- 1 Minimum 1 to 2 Gm. of protein per kg. of optimum body weight
- 2 Optimum 2 to 3 Gm. of protein per kg. of optimum body weight

II Sufficient Calories

1 For an adult

- 1 At complete rest 25 calories per kg. of optimum body weight per day
- 2 With very slight activities 30 calories per kg. of normal body weight per day
- 3 With light exercise 35 to 40 calories per kg. of normal body weight per day
- 4 With moderate exercise 40 to 45 calories per kg. of normal body weight per day
- 5 With hard muscular labor 45 to 50 calories per kg. of normal body weight per day

B For a child

- | | | |
|----------------|--------|---|
| Under 1 year | 100 | } Calories per kg. normal body weight per day |
| 1 to 2 years | 100-90 | |
| 2 to 5 years | 90-80 | |
| 6 to 9 years | 80-70 | |
| 10 to 13 years | 70-60 | |
| 14 to 17 years | 60-45 | |

- III Adequate Amount of Minerals
 - A Calcium Milk included in the diet
 - 1 For an adult 8 to 12 ounces per day
 - 2 For a child 16 to 32 ounces per day
 - B Iron Fruits, vegetables, eggs, meats, whole grain cereals
 - C Phosphorus Milk, eggs, cheese, meats, fruits, vegetables
- IV Abundance of Vitamins
 - I Vitamin A Butter, milk, cream, leafy vegetables, cod liver oil
 - B Vitamin B Fruits, vegetables, whole grain cereals, yeast, milk
 - C Vitamin C Fruits and vegetables, particularly citrus fruits and tomatoes. Include some raw fruits or vegetables 2 or 3 times a week, if possible every day
 - D Vitamin D Egg yolk, butter, cod liver oil
 - E Vitamin G Milk, egg, liver, meat, yeast
- V Sufficient bulk to stimulate normal bowel movement
 - I Two fruits and 3 vegetables or
 - B Three fruits and 2 vegetables
 - C Whole grain cereals. One serving of a whole grain cereal may be substituted for 1 serving of fruit or vegetable
- VI Water Six to 8 glasses in addition to amount in foods
- VII Maintain a careful balance of food nutrients

If the special diet prescribed is one on which the patient will remain for only a short time, the question of adequacy is not so important. It is a well-known fact that children and adults have developed deficiency diseases while on a special diet which has been prescribed and the doctor has forgotten to take the patient off the diet until the damage has been done. Thomas T. Mackie² cites a patient who was admitted to the hospital with intestinal hemorrhages because he had been on a colitis diet, low in vitamin C for too long a time. The blood count

had fallen to two million. After vitamin C was given the bleeding ceased at the end of a week. W. C. Alvarez³ says that "he sees no valid reason why a patient with ulcer should not be given meat and fruit juices." He follows the policy of putting an individual on a diet for a few days. If no improvement is shown, he stops the diet. It may be a wrong diagnosis. He advises dietitians to take a "middle of the road attitude" especially toward food sensitiveness. He has seen a patient brought into a hospital too weak to stand up as a result of being on an elimination diet. The patient was placed on 3 good meals a day and improved. The trouble was not food sensitiveness but domestic trouble.

In 1935 Gray reported the use of the low calcium diet for the treatment of lead poisoning. This year we read of newer concepts of treatment as reported on by I. Gray and I. Greenfield⁴. They now contend that a high calcium diet is being used with success. The phosphorus intake must be adequate. The patient should be kept on the diet no longer than 7 to 10 days.

A report on Addison's disease in this section shows an improvement over the work reported last year. A test to determine whether a patient really has Addison's disease is given. This test has been used with the desired results in the hospital where the Reviewers are located.

The patient with anemia still responds to liver therapy, and anorexia to vitamin B. Vitamin B concentrates commonly used are Bemax and Vegex. The diabetic diet has remained about the same. Prepared diabetic foods continue to disappear. Diet for the infant with eczema is covered once more, as well as rheumatism and gout. Last year a report was given by some English doctors on schizophrenia. This year a report

is given on some similar work in this country.

Urinary calculus is still being treated with the high vitamin A, acid or alkaline ash diet. Biophotometer tests are now used to determine whether a patient is utilizing adequate amounts of vitamin A. C. C. Higgins⁵ reports on his work. The raw apple diet is being replaced by the use of pectin, as shown in the article by G. Washburn⁶ on "The Use of Pectin Agar Preparation in the Treatment of Infantile Diarrhea." The apple had its disadvantages, she says. Certain times of the year it was very scarce. The diet in which it was used was very low in calories. It was difficult to feed to the infant. The introduction of the use of the pectin agar preparation is much more practical. The preparation is made of a mixture containing pectin (about 3 times that found in the apple), and agar agar as a source of bulk. The agar does not liquify at body temperature, therefore it passes through the intestine as bulk. Dextrimaltose is the main source of carbohydrate. These are all mixed together and will keep indefinitely. When ready to use it is mixed with milk. To this may be added more sugar for calories, cream, eggs and so forth. These infants often need the extra calories because they have lost much weight due to the diarrhea.

The Importance of an Adequate Diet—J. S. McLester⁷ speaks of the great difference today in dealing with the very sick person, in comparison to those of the past. The condition of patients was often made worse by too strict regulation of diet. He compares the very ill, undernourished typhoid patient with one today. Fed only broth and milk, the patient became desperately ill. Today the patient is given a diet meeting all his nutritive requirements. The difference in mortality is quite striking. The

whole treatment of Bright's disease was changed when it was discovered that low plasma protein was a very important factor in the treatment of glomerular nephritis. Examples are given of dogs who received a liberal protein intake, and whose urea clearance was higher than when the protein intake was low. Farr is mentioned, who worked with children having nephroses. These children showed a higher urea clearance and creatin clearance when they were given liberal amounts of protein. The belief in days gone by, that milk was not a protein, probably saved many people who had been placed on diets not allowing any eggs or meat.

The old story about the importance of sparing the kidneys in hypertension and nephrosclerosis is changing. McLester advises us not to carry protein restriction too far. The early arterial disease so common among diabetics has been reduced by a more liberal diet. Since more carbohydrate is now allowed, no one will dispute the fact that diabetics are a much more happy group of people.

Resistance to infection is most common in persons who are on an abundant diet. Lack of vitamin C plus an infection may cause a case of rheumatic fever. When the vitamin intake is made abundant, the individual usually responds with good health and plenty of vitality. However, he goes on to say, that too much stress must not be laid on the vitamins. Other food factors are also very important. The work of Rose is mentioned concerning the 21 amino acids which he worked with, but found that he could not support growth with them. Later in his search, he found a new amino acid to which he gave the name threonine. When this was added to his mixture, a substitute for protein was found. McLester believes that man re-

quires much more protein in his diet than is generally thought today.

Fats should never be eliminated from the diet entirely. Experiments with rats resulted in a skin disease when they were kept on a fat-free diet. Successful gestation and lactation were dependent upon the intake of certain essential fatty acids. He says that fats should not be eliminated for "safety's sake."

Inadequate diet may be the cause of many discomforts, such as lack of appetite, vague pains, digestive disorders and so forth. The rich are found to be victims as well as the poor. Even such a condition as atherosclerosis may be laid to inadequate diet. With an adequate diet especially rich in protein and the vitamins, McLester believes that much sickness will disappear and people will gradually develop better food habits.

Nutrition - Minerals — Mary A. Brady⁶ quotes McLester, "To emphasize any one food factor or group of factors is a dangerous thing. It is apt to lead to one of the greatest causes of nutritional failure in America, food faddism. I hasten to add that an exception should be made in the case of milk. The teaching should include instruction in the value of each of the foods and the place each should have in the diet, and emphasis should be placed always on the danger of the one-sided diet." This is quoted because while she emphasizes a few food factors in her paper, she does not want any one to think that they must concentrate on those.

The minerals calcium, iron, and iodine are emphasized. The diet must be planned wisely or these elements will be deficient. McLester says that milk must be stressed. One quart of whole milk or about 5 ounces of Cheddar cheese daily supplies enough calcium for the needs of the growing child. There is no other

way for the adult or child to meet his requirement.

The availability of iron is just as important as the iron content of food, in fact, it is more important. Some foods have a very high iron content, but only a small amount is available.

Dr. Elvehjem and his coworkers at the University of Wisconsin have given us some tables including the available iron in various common foods.

	Per cent
Egg yolk	100
Heart—Pork	86
Beef	70
Liver—Pork	66
Beef	70
Steak	50
Oysters	25
Cream of wheat...	No available iron
Soy bean	80
Navy bean	60
Oats	57
Wheat	47
Yeast	47
Apricots	50
Parsley	22
Spinach	20

The egg has 100 per cent available iron, or 1 mg. which is about $\frac{1}{4}$ of the day's need for a child. The fact that a liberal calcium intake makes for better utilization of iron is another good reason for including 1 quart of milk in the diet every day. A dietary study showed that the free use of vegetables, whole wheat bread, and cheaper fruits with milk resulted in a gain of 30 per cent in the iron content of the diet.

Our requirement of iodine is only 1 part in about 3,000,000 parts of body weight. The iodine which we get comes through our drinking water or the use of sea foods such as salmon, cod fish, oysters and cod liver oil. It has been found that milk, potatoes, and oats grown in goitrous regions have more iodine in them than is found in other foods in those same sections.

FEEDING THE NORMAL INFANT AND CHILD

Dr. Katharine K. Merritt⁴ states that Bowles' statistics show that the "grown children of today entering colleges and universities in the United States seem to average 2 inches taller and weigh some 7 pounds more than did their parents and grandparents who entered the same schools." The reasons seem uncertain for the increase in weight and stature, but "better food in more abundance and in greater variety is one of the probable causes."

It is of utmost importance that there should be correct feeding in the first few weeks of life. Breast feeding is the ideal régime providing that there is an adequate amount. Dr. McIntosh feels that unless the infant receives 10 ounces of breast milk in 24 hours, after a trial of 2 or 3 weeks, nursing is not worth while continuing. "There are certain immune bodies which are transferred to the infant through breast milk, but this transference does not explain many of the phenomena of immunity which we see in the newly born. From the point of view of immunity alone, it is wise to have the baby breast-fed for at least the first few weeks of life, if this is reasonably possible." If the physical condition of the mother is poor, or if it is a strain to nurse the infant, or if there is an economic pressure such as the mother having to go to work a few weeks after the baby's birth, then weaning of the infant is certainly indicated.

The infant is very unusual if he does not do as well on artificial feeding as on breast milk providing the formula is properly constructed. "Proper construction" means. First, the milk should be boiled, no matter what kind of milk is used. second, the calories should be sufficient. The number of required calories

can not be fixed by certain rules; the infant's formula should be constructed so that he will gain 6 to 7 ounces a week in the first months of life, and 4 to 5 ounces a week in the last months of the first year. "For the average infant, 50 to 55 calories per pound of body weight is sufficient during first months of life."

Dr. Merritt says that it is their custom on the "new-born service" to put all babies weighing 7 pounds or over, on 5 feedings 4 hours apart. The schedule continues until the age of 3 or 4 months, then most of them can go on a schedule of 4 feedings. There cannot be an over-emphasis of the importance of regularity in feeding time and rigid adherence to a 4-hour interval.

There is an increasing use of evaporated milk in infant feeding. Evaporated milk has several advantages: (a) It is cheaper than the same amount of whole milk; (b) it is completely sterile; (c) it is more digestible than fresh milk because it has a smaller curd which is softer and more gelatinous than that of any other heated milk; (d) it is easily carried when traveling and can be carried to distant places where fresh milk is unobtainable; (e) it is very valuable for use when a concentrated diet feeding is desired, especially for premature infants and those suffering with chronic nutritional disturbances. "An ounce of evaporated milk contains approximately 43 calories, or a little more than twice that of fresh milk."

The kind of sugar used in a formula is only a matter of personal choice. Apparently there is no advantage in giving monosaccharides. "Of the double sugars, lactose theoretically would seem the best to use, since it is the carbohydrate of both breast and cow's milk, but practically there seems to be little advantage in using this type of sugar." Usually

cane sugar is the most satisfactory, it is inexpensive and always available.

If the infant should have diarrhea and large amounts of sugar are indicated, a polysaccharide or a mixture of sugars may be advisable. Karo corn syrup (half of which is a dextrin, and half malt sugar and dextrose) is one of the cheapest forms of carbohydrate.

In the early weeks of life of an infant vitamins should be considered as part of the dietary. Merritt says that at about the fifth day $\frac{1}{2}$ teaspoonful of cod-liver oil daily should be added to the dietary. Usually on the tenth day when the infant leaves the hospital it is increased to 1 teaspoonful and is rapidly increased to 3 teaspoonfuls a day at about 5 or 6 weeks.

At about the fourth or fifth week orange juice is added.

There is considerable difference of opinion as to the age at which solid food should be given. Cereal may be introduced at the third or fourth month of life, vegetable purée, egg yolk and stewed fruit at the fourth and fifth month. Scraped beef and liver can be added at the sixth month. The greatest advantage of this early feeding of cereals and vegetables is to get the child used to food other than milk, thus becoming familiar with the feeling of solid food in the mouth before he is expected to chew.

An infant usually gets teeth at 6 months of age, if he is given nothing but liquids up to 9 months or a year it is often very difficult to get him to take solid foods, but it is usually fairly easy to give young babies any sort of food. Merritt says that her faith in the digestive ability of infants has been greatly strengthened since she gave a group of newborn premature infants finely ground raw liver in with the formula with no unfavorable results.

A decision as to what and how much babies should eat "has been thrown into

discard" by Dr. Davis, who originated the method of self-selected diet for infant's likes and dislikes can be made a vegetables, cereals, fruits, sweet and fermented milk, and sea salt was offered to a group of infants at about 8 or 9 months of age or the "weaning age." As soon as the dishes were emptied they were refilled and each infant ate what and how much he pleased without interference.

Merritt states that "Dr. Davis thought her experiments suggested that the infants' likes and dislikes can be made a help and not a hindrance to his feedings. She questions whether it is a sound practice to specify too rigidly regarding the quantity of food to be eaten, and the manner of eating it, or that interference and diversion should necessarily accompany each meal." The importance of such experiments is the fact that we cannot decide for a child how much he should eat and then force it down. He should be offered a reasonable amount of food and left to take it or leave it. Forcing and nagging are definitely bad physically and psychologically.

If a good weight has been reached by the infant at the age of 6 months, he can be put on 3 meals a day; the hours so arranged as to suit the convenience of the family, but there should be approximately a 5 hours lapse between meals. Breakfast may consist of cereal, toast or zwiebach, stewed fruit and 8 ounces of milk, at dinner he may have egg yolk or scraped beef or liver, green vegetable purée, baked potato or rice or macaroni (provided the infant is not overweight, otherwise another green vegetable should be substituted for the starchy vegetable), and a dessert of stewed fruit, or junket, or custard (made with egg yolk). Milk at dinner can be given in varying amounts from 4 to 8 ounces depending on the appetite of the

child. If he takes the milk instead of the solid food the milk should be cut to the minimum and be taken at the end of the meal or omitted altogether. Supper may be the same as at breakfast. If the child is much overweight it is recommended that a green vegetable be substituted for the cereal at the evening meal. A substitution for the stewed fruit may be a dessert made of milk, or milk and egg yolk.

There should be more variety by the ninth and tenth month, and if the child is hungry an egg yolk may be added at breakfast. Dr. Merritt feels that at 1 year of age the "white supper" as Dr. Kerley describes a meal consisting of cereal, milk and toast, should be abandoned, or other food articles added. Some protein foods may be introduced. A whole egg may very cautiously be added, but the white of egg should always be given in very small amounts at first. A green vegetable may be given, also macaroni and rice may be interchanged with cereal. At about 18 months of age, bacon may be added to the breakfast. If the child is hungry he may have both bacon and egg, if not, alternate egg and bacon. From this time on a protein food may be given at each meal. It is preferable that the type of protein be varied, if egg is served at breakfast and meat at dinner, then fish (preferably starting with the coarser fish, such as cod or halibut), chicken or liver may be served at supper. Variety is also added by serving cottage cheese and peanut butter.

It seems to be a popular idea that meat and eggs are "heavy" foods, and that they heat the blood. It is not realized that protein foods play an important part in the body metabolism and that a growing child requires relatively more protein than an adult. There is much greater danger in not giving enough than in giving too much. In fact the

excess amino acids beyond body requirements is burned in the body as fuel.

One should purée and strain vegetables as long as the child cannot chew, but he should be given a chance to chew as soon as he can be reasonably expected to. It is a custom at 6 months of age to give graham crackers or zweibach to exercise the incisors. A child from 12 to 18 months should be given foods that are chopped, not puréed, and soon after he may have his food served as an adult. He should also have at this age raw food such as lettuce, tomatoes, apples, and pears. "It is essential to dental health to have coarse food which requires thorough chewing." Whole wheat bread and brown cereals should be given preference over white bread and cereals.

A child of 3 years of age should be able to eat a meal which any adult can, but with quantities and choice of food suited to his digestive capacity.

BREAKFAST

Orange juice, fresh fruit or stewed fruit
Egg and bacon
Cereal (if the child is very hungry and not overweight)
Whole wheat toast
Milk—8 ounces

DINNER

Meat (lamb or beef), chicken or fish
Rice, macaroni or potato
Any vegetable and salad of greens
Dessert made of milk, eggs or fruit
Whole wheat toast
Milk—6 to 8 ounces (in the child is still hungry at the end of the meal)

SUPPER

Eggs, chicken, fish or meat, or cottage cheese, or peanut butter sandwich
Potato, rice or macaroni
Green vegetable or salad
Stewed or raw fruit
Toast
Milk—4 to 8 ounces

Broth has not been mentioned in any of the diets for it is of negligible caloric

value and fills up the stomach, leaving less room for the more important foods. When the child grows older, in order to give variety and lessen the monotony, cream soup may be served at supper. In the cream soup, part of the child's milk can be used and then less of the main dish given.

ADDISON'S DISEASE

H. H. Cutler, M. H. Power and R. M. Wilder¹⁰ state that it having been demonstrated by Wilder and Kendall and others that administering potassium to patients with Addison's disease would cause excretion of sodium and chloride and precipitate crisis, they suppose that urine examination for sodium and chloride under standard conditions of administration of potassium and the use of a diet low in salt might give more "reliable information about adrenocortical function than frequently is obtained by examination of the blood."

The low salt diet used in the examination provides 0.95 Gm. chloride ion, 0.59 Gm. sodium and 4.1 Gm. potassium. The fluid intake the first day was not measured, but a liberal amount of water was requested.

The afternoon of the first day extra potassium was given as potassium citrate, the dose "representing 33 mg. of potassium per kg. of body weight (42 mg. of potassium citrate per pound)."

The fluid intake for the second day should equal 40 cc. for each kg. of body weight and the dose of potassium citrate is repeated. "On the third day 20 cc. of liquid per kg. of body weight was given before 11 A. M. At 12 noon of this third day the examination ended, except in those cases in which the period of deprivation of salt was extended in order to obtain additional evidence of the state of adrenocortical function."

The following is the diet used in the Standardized Diagnostic Procedure for Addison's disease.

	Break- fast Gm	Dinner Gm	Supper Gm	K Gm	Na Gm	Cl Gm
Vegetables						
Canned Tomatoes		90		0.27	0.01	0.34
Lettuce		10	10	0.06	0.005	0.015
Fruit						
Peaches		100		0.125	0.022	0.004
Oranges	100			0.2	0.012	0.006
Grapefruit			100	0.2	0.004	0.005
Bananas			100	0.4	0.034	0.125
Vegetables						
Canned Peas			100	0.125	0.013	0.024
Baked Potato		100	100	1.000	0.042	0.076
Bread, Salt Free	50	30	30	0.11	0.073	0.127
Jello		150				
Butter, Salt Free	10	10	10	0.003	0.021	0.049
Cream, 20%	25	25	75	0.158	0.044	0.1
Milk			200	0.3	0.102	0.212
Coffee, Medium	300	200		0.5		
Eggs	1			0.07	0.071	0.053
Beef, Lean (weigh before cooking)		75	50	0.465	0.131	0.117
Jelly	20	20	20	0.076	0.008	0.002
Total				4.062	0.592	0.949

ADEQUATE DIET IN WHICH POTASSIUM CONTENT DOES NOT EXCEED 2 GRAMS

Foods	Gm.	Approx. Measure
Breakfast		
Orange or grapefruit	100	1 average size serving
Cream of wheat	15	1 average size serving
Egg	50	1
Bacon	10	2 small strips
Bread, white—may be toasted	30	1 slice
Butter	10	1 square
Cream	90	½ cup scant
For Second Meal:		
Meat, specially cooked	75	1 fairly large serving
Potato, specially cooked	100	1 serving
Raw vegetable (lettuce, celery, tomato, cabbage, Swiss chard or watercress)	100	1 serving
Mayonnaise	15	1 tablespoon
Bread, white	30	1 slice
Butter	20	2 squares
Fruit (apples, pears, strawberries or tangerines)	100	1 serving
Cream	30	2 tablespoons
Milk	200	1 glass
Cheese	20	1 cubic inch
For Third Meal.		
Egg	50	1
Polished rice (weigh dry)	25	1 serving (½ cup)
Vegetables, specially cooked (asparagus, carrots, onions, turnips or squash)	100	1 serving
Bread, white	30	1 slice
Butter	20	2 squares
Fruit (apples, pears, strawberries or tangerines)	100	1 serving
Cream	30	2 tablespoons
Milk	100	½ glass

With the knowledge that patients suffering from Addison's disease are definitely sensitive to potassium, Sister Mary Victor¹¹ has prepared a diet low in potassium. The potassium content of an average diet is between 4 and 5 Gm. each day. If, however, one uses a liberal amount of foods and food accessories rich in potassium as soups, broths and gravies containing meat stock or meat extract, catsup, mustard, and other seasonings, dried legumes, nuts, tea, coffee, chocolate, Postum, bran, dried fruits and whole grain cereals, the normal amount of potassium may be more than doubled.

It has been found that the daily intake of 4 Gm. of potassium affects unfavorably the course of Addison's disease therefore a diet containing half this amount of potassium has been planned

"To construct a diet restricted in potassium it was found necessary" (a) To limit the selection of bread, cereal, and sugars to the highly refined products, (b) to use, moderately, milk, meat, fruit, vegetables and condiments, and (c) to include vegetables and meats prepared according to a special method whereby their content of potassium is reduced to such an extent that they may be used with safety.

The special method of preparing vegetables and meats consists of cutting the vegetables into small pieces and cooking them in 6 to 8 times as much water as ordinarily needed in cooking vegetables. The potassium in these vegetables is reduced from 60 to 70 per cent without a "concurrent diminution of palatability." Meat is cut into small pieces and cooked in a so-called parchment paper with

about 1 part of meat to 6 to 8 parts of water. The potassium content of the meat is reduced about one-fourth without detracting from the other nutrients and extractives which give flavor to meat.

The diet is fully adequate in respect to calories, protein, and minerals. The caloric value is 2812 and is in excess of the amount (35 calories per kg of body weight) given as a standard for an average-sized man doing moderately heavy work. The calories may be adjusted to maintain or produce normal body weight by the addition or subtraction of such foods as butter, mayonnaise and refined sugar. By the substitution of whipping cream (40 per cent butter fat) for coffee cream (20 per cent butter fat) the caloric value of the diet may be increased.

However, the diet is deficient in vitamin B₁. Sufficient vitamin B₂ is found in the milk, eggs and cheese and green vegetables. Because of the highly refined cereals and extra cooking of the vegetables vitamin B₁ is deficient and should be made up in a vitamin B₁ concentrate low in potassium. One milligram of thiamin chloride is suggested by Sister Mary Victor.

All foods should be weighed or measured carefully. One cup of weak coffee and 2 cups of weak tea are allowed daily. Salt may be used in generous amounts. Pepper and vinegar may be used in moderation. White sugar may be used liberally. Gelatin, either plain or flavored, can be used in salad or desserts. Carbonated beverages, such as ginger ale, coca cola and also fruits prepared from synthetic beverage powders or crystals may be used. Any of these beverages may be used to put in the "extra" salt usually prescribed.

By the use of this plan as a basis and by the substitution of different foods as given in the lists of foods for substitutes

by Sister Mary Victor the diet may be varied and attractive menus planned.

GOUT

J. H. Talbott and F. S. Coombs¹² report a metabolic study made on some patients with gout. They remind us that the protein content of the diet and "the alcoholic content of fluids have been the battleground for most discussions of the treatment of the chronic form of gout."

These men tell us that the importance of excluding foods with a high purine content from the diet has been over-exaggerated. They report a patient on a diet low in purine in the hospital. The patient had 12 attacks of acute arthritis and severe gout in 27 days. He left the hospital and ate the foods to which he had been accustomed, disregarding the low purine diet. He had 7 acute attacks of arthritis and 7 attacks of severe gout in 18 days. Similar data was obtained on another patient. Observations showed that the number of attacks a year and of days spent in bed during the time the patient was on a low purine diet was about 10 times that while the patient was on a liberal diet including as much meat as he desired. A large fluid intake is stressed and reduction of the patient if he is overweight. A well-balanced, adequate diet is suggested to take the place of the old low purine diet.

HYPERTHYROIDISM

S. Soskin and I. A. Mirsky¹³ report on a patient who refused operation in a case of hyperthyroidism. Instead he was given a high fat diet. During a control period, the patient received a diet consisting of protein 80 Gm., fat 80 Gm. and carbohydrate 400 Gm., a total of 2640 calories. After a period of 2 weeks

the patient was placed on a diet consisting of 90 Gm. of protein, and 230 Gm. of fat and 90 Gm. of carbohydrate. This was a total of 2790 calories. For a period of 23 days, 3 Gm. of cholesterol was added to the diet in the butter. No other treatment except rest in bed was used. Improvement was noted from the start. The addition of cholesterol was discontinued, there being no need for it. The patient went home after a period of 2 months and continued on the high fat diet. The authors feel that this one case does not justify a conclusion. They do feel that it may be worthwhile for others to try it, should a patient refuse surgical treatment.

INFANTILE ECZEMA

L. W. Hill¹⁴ reports on the dietetic treatment of infantile eczema. He says that dietetic treatment is of value only in the treatment of seborrheic and atopic dermatitis. In other types of eruptions it may not be affected at all by diet.

In the first place he warns against obesity if the baby has seborrheic dermatitis. Moderate underfeeding may have the desired results. The omission of any one food is not indicated. He suggests a diet relatively low in fat and high in protein. The following is a prescription which he gives for a feeding formula low in fat and high in protein:

Two per cent milk ..	20 ounces
Water .	9 ounces
Karo corn syrup	2 tablespoons
Powdered casein	4 level tablespoons

When treating the infant with atopic dermatitis, he suggests the skin tests as a means of finding out if the infant is allergic. When planning the diet for this type of infant one should be guided by the results. If no skin tests are made the following diet may be used which may meet the need of the infant:

Evaporated cow's milk or goat's milk for mild cases or for any infant whose nutrition is poor.

A milk free food for moderately severe or severe cases if the nutrition is good.

Corn meal or oatmeal.

Carrots or string beans.

Banana.

Fish oil.

Ascorbic acid.

If the baby is too thin, he should be made to gain weight. If he is too fat, he should be made to lose some weight. If he has been taking too much milk, it should be reduced. If he has been taking milk from cows such as the Jersey or Guernsey, the milk supply should be changed to some source where there will not be such a high fat content. There is no need for changing sugars. Hill stresses the adequate diet, as so many authorities do today. His health should be considered first, and the child should be well nourished regardless of offending foods. Usually substitutes for offending food may be found. Infants who are unable to tolerate cow's milk can often take goat's milk with no ill results, or evaporated milk may agree. The author does not believe that there is anything as yet which will satisfactorily treat infantile eczema.

SCHIZOPHRENIA

Sylvia E. Waide and Donald W. Hastings¹⁵ have compiled a dietary régime, in connection with giving of large doses of insulin. The treatment by insulin is divided into 4 stages: (1) Introductory phase, the patient is gradually given a dose of insulin of sufficient strength to produce coma; (2) shock phase, the patient is put into insulin shock daily with the exception of Sunday, (this phase lasts on the average of from 6 to 8 weeks); (3) rest phase, this is merely the Sunday rest; (4) transition phase,

after the shock phase has run a long enough course as judged by the physician, the insulin dosage is reduced daily—this is completed in 5 to 6 days.

The patient must have enough food to cover the amount of insulin that has been injected, or else hypoglycemia and the symptoms attendant on it will appear and the patient will have an "aftershock."

During the first few months Waide and Hastings gave high caloric diets with the result that with 6 to 8 weeks of treatment the patients gained on an average of 20 pounds. The following is the high caloric diet plan followed

MORNING GROUP

(Time and calories are approximate)

- 1 No breakfast.
- 7 00 A M -2 Insulin given
- 11 00 A M -3 Interruption of hypoglycemia with 50 cc. of 25 per cent glucose intravenously. This was followed in 5 minutes by
- 11 05 A M -4 Double tray (1600 calories)
- 12 30 P M -5 Normal lunch (800 calories)
- 5 00 P M -6 Normal supper (1000 calories)
- 9 00 P M -7 Extra nourishment (400 calories)

AFTERNOON GROUP

(Time and calories are approximate)

- 7 00 A M -1 Light breakfast (350 calories)
- 2 No lunch
- 1 00 P M -3 Insulin given
- 5 00 P M -4 Interruption of hypoglycemia with 50 cc. of 25 per cent glucose intravenously. This was followed within 5 minutes by
- 5 05 P M -5 Double tray (1600 calories)
- 6 30 P M -6 Normal lunch (800 calories)
- 9 00 P M -7 Normal supper (1000 calories)
- 10 30 P M -8 Extra nourishment (400 calories)

This dietary régime was very satisfactory in that there were no "after-shocks," but there were two difficulties that arose. (a) It was difficult for the patient to eat a double tray on awakening from insulin shock. (b) the patient gained too much weight

On consideration, Waide and Hastings resorted to a modification of the above régime. On the assumption that it requires 1 unit of insulin "to store" 2 Gm. of carbohydrate they made a solution of cane sugar in water using 10 Gm. of sugar per ounce of water and flavored it with lemon juice. The amount of the solution given depended on the insulin dosage. For example, 90 units of insulin were given, therefore it would require 180 Gm. of carbohydrate "to neutralize it." The solution contains 10 Gm. of carbohydrate to the ounce. The patient would then receive 18 ounces of the solution to meet the insulin requirements. In order to be sure of the amount, an additional 3 or 4 ounces of the solution were given plus 1 or 2 slices of bread and jelly. By experience, it has been found that a patient can not comfortably take care of more than 30 ounces of the solution. Since 30 ounces of the solution takes care of only 150 units of insulin, the patients receiving 150 units of insulin receive 30 ounces of the solution and a breakfast of 400 to 500 calories. This is the substitution for the "double tray" of 1600 calories.

The feeding schedule for the morning group of patients is as follows

- 1 No breakfast
- 7 00 A M -2 Insulin given
- 11 00 A M -3 Interruption of hypoglycemia with 50 cc. of 25 per cent glucose intravenously. This is followed within 5 minutes by
- 11 05 A M -4 Cane sugar solution (to meet the insulin dosage requirement plus a slice of bread and jelly. (For dosages over 150 units of insulin, the patients receive a normal breakfast in addition to the 30 ounces of the sugar solution.)
- 12 30 P M -5 Normal lunch
- 5 00 P M -6 Normal supper
- 9 00 P M -6 Extra nourishment

The extra nourishment at night can be given in the form of the cane sugar solution 10 to 12 ounces.

Under the modified diet the patients gain on an average of 8 to 10 pounds, but it must be expected that there will be some gain because of the extra caloric intake demanded by the treatment

TUBERCULOSIS

D Barker¹⁶ stresses the importance of the normal well-balanced diet in considering diet therapy. She feels that all special diets should be only a variation of the normal, with restrictions or additions as the case may be. Resistance to bacteria and toxins is naturally increased by increasing the intake of calories and vitamins. This is done by giving extra fruits, vegetables, and milk.

She classifies the diets used at the sanatorium of which she speaks

A general diet for the ambulatory patient

A soft or low residue diet for the patient with high elevation in the temperature or for the patient with tuberculous intestines

A cold liquid diet for hemorrhage cases

Liberal amounts of cream, butter and milk are included to raise the caloric and vitamin content

For breakfast, the patient may eat any fruit in season, hot or cold cereal, bacon or ham and eggs, with an ample supply of cream. Midmorning, midafternoon and evening nourishments should consist of milk, milk drinks or fruit juice. These in-between nourishments should be encouraged.

The diet for the patient on a low residue diet is planned from the general diet, changing the consistency, that is using puréed vegetables, strained cereals, creamed meat, soft cooked fruits, fruit juice, gelatins, custards and simple puddings. When the restriction on diet will not last long, there is no necessity

to worry about adequacy. The liquid diet is not adequate, but is never used over a long period of time. Palatable liquids ranging from iced fruit juices to jellied broths are given. The diet is then increased to one which involves a minimum effort to masticate and digest. If flatus is present, a low roughage diet similar to the one used in gall-bladder disease is given.

If the disease is complicated by diabetes, the usual restriction on carbohydrate must be given. The fat may be increased to add calories to prevent loss of too much weight. The nephritic patient will be restricted to a small amount of salt. The nonprotein nitrogen will determine the protein intake. Elimination diets will be given to the allergic individual to determine to what foods and extent he is allergic. Occasionally a reduction diet may have to be given, but it is suggested that the weight loss be limited to 2 pounds a week. Food fads must not be tolerated. Following are some sample menus used at the sanatorium. A selection of the entrees is given.

DINNER

Creole soup	
Baked haddock, tartar sauce	
Pot roast of beef	Orange fritter
Meat pie with vegetables	
Mashed potatoes	Green string beans
Cabbage and pineapple salad	
Lemon cream pie	Drink

SUPPER

Sweet pickles	
Grilled club steak with green onions	
Creamed tuna on toast	
Baked potato	Buttered peas
Shred tomato salad	
Fruit	Jelly roll
Drink	

DINNER

Vegetable soup	
Roast pork leg with cranberry jelly	
Boiled beef with horseradish	
Chicken gizzards with rice	
Mashed potatoes	Broccoli
Hearts of lettuce	French dressing
Brown Betty pudding	Drink

SUPPER		
	Grilled veal chops	
	Fried ham and eggs	
	Creamed asparagus on toast	
Baked potato		Spinach
	Cottage cheese salad	
	Hot biscuits and jelly	
Fruit	Cookies	Drink
DINNER		
Olives	Chicken broth with noodles	
	Roast young chicken	
	Prime roast beef au jus	
Mashed potatoes	Buttered carrot and peas	
	Pear bar le duc salad	
	Hot dinner rolls	
Vanilla ice cream, cake		Drink
SUPPER		
Sweet gherkins	Celery hearts	
	Oyster stew	
Baked Virginia ham	Cold roast beef	
	Buttered rice with cream	
	Sliced tomato salad	
	Hot dinner rolls	
Fruit and cookies		Drink

POTASSIUM IN THE DIET

Violet Ashkins and R. L. Zwemer¹⁷ in trying to reach a certain potassium content for 24 hours have selected menus for the variability in the potassium content and the adequacy in calories, carbohydrate, fats and proteins. Mineral and vitamin concentrates may be added without altering very much the purposes of the selected diet.

"It should be noted that in most cases the potassium values are for foods as purchased and that their preparation, particularly boiling, will lower the ultimate potassium concentration. Most investigators agree that fresh skeletal muscle of mammals has approximately 0.5 per cent potassium, so that this is the figure used for uncooked meat. With the exception of tea, the rest of the potassium figures are from Sherman. In giving the relation of common meas-

ures to grams, Waller and Bridges were used."

TABLE 1

FOODS ARRANGED ACCORDING TO POTASSIUM CONTENT

A, Meats, etc., *B*, vegetables, *C*, cereals, *D*, fruits, *E*, beverages, *F*, miscellaneous

GROUP 1—0.0 to 0.1 per cent K. *A*, Cheese, oysters, *B*, okra; *C*, wheat gluten, white rice, *D*, blueberries, cranberries, huckleberries, pomegranate, watermelon; *E*, tea, cider, huckleberry wine, milk (buffalo, human, mare). *F*, butter, sugar

GROUP 2—0.1 to 0.2 per cent K. *A*, bacon, eggs, round clams, *B*, asparagus, cucumbers, eggplant, green peppers, leeks, onions, summer squash, sweet corn, *C*, bread (rye and white), crackers, farina, hominy, macaroni, *D*, apples, blackberries, gooseberries, grapefruit, grapes, lemons, oranges, pears, raspberries, strawberries, *E*, juices of foregoing fruits, buttermilk, coconut milk, cream, milk (cow, camel, goat, sheep), *F*, jellies and jams, vinegar, whey

GROUP 3—0.2 to 0.3 per cent K. *A*, clams (soft, long), *B*, cabbage, carrots, cauliflower, peas (fresh), radishes, stringbeans, tomatoes, watercress, *C*, barley (pearled), corn meal, millet, whole wheat flour, bread (Boston brown, graham, whole wheat), *D*, apricots, breadfruit, cantaloupe, cherries, citron, currants, mangoes, muskmelon, peaches, persimmons, plums, whortleberries, *E*, juices (apricot, cherry, tomato), *F*, capers, maple syrup, wheat germ

GROUP 4—0.3 to 0.4 per cent K. *B*, beets, Brussel sprouts, celery, chard, corn (mature), endive, kohlrabi, lettuce, mangold, mushrooms, pumpkin, romaine, rutabagas, turnips, turnip tops, sweet potatoes, winter squash, *D*, figs, guava, limes, mammee, pineapple, rhubarb, *F*, coconuts, honey, pecans, walnuts

GROUP 5—0.4 to 0.5 per cent K. *A*, caviar, fish, red meats, *B*, horseradish, potatoes, truffles, *C*, barley (whole grain), flour (graham, rye), rye (whole grain), wheat (whole grain), *D*, bananas, *F*, dandelion

GROUP 6—0.5 to 0.73 per cent K. *A*, meat peptone, solid meat extract; *B*, beans, cabbage greens, cowpeas, lentils, lima beans, lupines, olives, parsnips, spinach; *C*, cotton, flax, and linseed meal, wheat bran; *D*, dried fruits (*e.g.*, currants, figs, peaches, prunes, raisins); *E*, cocoa; *F*, almonds, chestnuts, chocolate, dried coconut, hazelnuts, molasses, mustard, paprika, peanuts, pepper

SAMPLE MENU CONTAINING 1 GM POTASSIUM

Food	Grams	Measure	Potassium
Breakfast			
Orange	100	1 weighed with skin	0.177
Farina	20	$\frac{1}{8}$ cup	0.024
Bread (white)	30	1 slice	0.032
Butter	14	1 T	0.0018
Milk	50	$\frac{1}{4}$ glass	0.072
Cream	50	$\frac{1}{4}$ glass	0.063
Sugar	13	1 T	
Cheese	50	$\frac{1}{5}$ " slice (5 lb. long loaf)	0.045
Macaroni	20	$\frac{1}{5}$ cup	0.026
Sweet corn	100	1 ear, 8" ($\frac{1}{2}$ cup)	0.113
Blueberries	100	$\frac{2}{3}$ cup	0.051
Bread (white)	30	1 slice	0.032
Butter	14	1 T	0.0018
Cream	50	$\frac{1}{4}$ glass	0.063
Supper			
Eggs	50	1	0.070
Asparagus	50	6—5" stalks	0.098
Apple	100	1 small	0.127
Bread (white)	30	1 slice	0.032
Butter	14	1 T	0.0018
Cream	50	$\frac{1}{4}$ glass	0.063

Totals. Approx P 53, F. 91, C 150, Cal 1631 Potassium 1.0994 Gm

SAMPLE MENU CONTAINING 2 GM POTASSIUM

Food	Grams	Measure	Potassium
Breakfast			
Orange juice	100	$\frac{1}{2}$ glass	0.182
Farina	20	$\frac{1}{8}$ cup	0.024
Eggs	100	2	0.140
Bread (white)	30	1 slice	0.032
Butter	14	1 T	0.0018
Milk	100	$\frac{1}{2}$ glass	0.143
Cream	100	$\frac{1}{2}$ glass	0.126
Sugar	13	1 T	
Dinner			
Cheese	50	$\frac{1}{5}$ " slice (5 lb. long loaf)	0.045
Potatoes	50	$\frac{1}{2}$ (2 $\frac{1}{2}$ " diam.)	0.214
Carrots	50	$\frac{1}{8}$ cup (drained)	0.123
Blueberries	100	$\frac{2}{3}$ cup	0.051
Bread (white)	30	1 slice	0.032
Butter	14	1 T	0.0018
Milk	100	$\frac{1}{2}$ glass	0.143
Cream	50	$\frac{1}{4}$ glass	0.063
Supper			
Egg	50	1	0.070
Corn, sweet	100	1 ear, 8" ($\frac{1}{2}$ cup)	0.113
Summer squash	100	$\frac{7}{10}$ cup	0.150
Pears	100	1 medium	0.132
Bread	30	1 slice	0.032
Butter	14	1 T	0.0018
Milk	100	$\frac{1}{2}$ glass	0.143
Cream	50	$\frac{1}{4}$ glass	0.063

Totals. Approx P 74, F 121, C 169, Cal 2061 Potassium, 2.0264 Gm

SAMPLE MENU CONTAINING 4 GM POTASSIUM

Food	Grams	Measure	Potassium
Breakfast			
Oranges	200	2, weighed with skin	0.354
Cornmeal	20	$\frac{1}{8}$ cup	0.043
Eggs	100	2	0.140
Bacon	20	2 slices ($1\frac{1}{2}'' \times 4\frac{1}{2}'' \times \frac{1}{8}''$)	0.034
Bread	60	2 slices	0.064
Butter	7	$\frac{1}{2}$ T	0.0009
Milk	200	1 glass	0.286
Cream	100	$\frac{1}{2}$ glass	0.126
Dried currants	30	$\frac{1}{8}$ cup	0.262
Dinner			
Meat or fish	50	Slice, $2'' \times 2'' \times \frac{1}{4}''$	0.250
Potatoes	100	1 ($2\frac{1}{2}''$ diam)	0.429
Peas	100	$\frac{3}{4}$ cup	0.285
Tomatoes	100	1 ($2\frac{1}{2}''$ diam)	0.275
Pears	100	1 medium	0.132
Bread	30	1 slice	0.032
Butter	7	$\frac{1}{2}$ T	0.0009
Supper			
Meat or fish	50	Slice $2'' \times 2'' \times \frac{1}{4}''$	0.250
Carrots	100	$\frac{3}{5}$ cup	0.287
Cauliflower	100	1 cup	0.222
Peaches	100	1 medium	0.214
Bread	30	1 slice	0.032
Butter	7	$\frac{1}{2}$ T	0.0009
Milk	200	1 glass	0.286

Totals: Approx P 86, F 87, C 219, Cal 1967 Potassium, 4.0057 Gm

SAMPLE MENU CONTAINING 6 GM POTASSIUM

Food	Grams	Measure	Potassium
Breakfast			
Banana (1 P)	100	$\frac{3}{4}$ cup or $\frac{1}{2}$ large	0.401
Cornmeal	20	$\frac{1}{8}$ cup	0.043
Eggs	100	2	0.140
Bacon	20	2 slices ($1\frac{1}{2}'' \times 4\frac{1}{2}'' \times \frac{1}{8}''$)	0.034
Bread	60	2 slices	0.064
Butter	7	$\frac{1}{2}$ T	0.0009
Milk	200	1 glass	0.286
Cream	100	$\frac{1}{2}$ glass	0.126
Dried raisins	50	$\frac{1}{8}$ cup	0.410
Dinner			
Meat or fish	100	2 slices $2'' \times 2'' \times \frac{1}{4}''$	0.500
Potatoes	100	1 ($2\frac{1}{2}''$ diam)	0.429
Winter squash	100	$\frac{7}{10}$ cup	0.320
Peas	100	$\frac{3}{4}$ cup	0.285
Peaches	100	1 medium	0.214
Bread	30	1 slice	0.032
Butter	7	$\frac{1}{2}$ T	0.0009
Milk	200	1 glass	0.286
Dried currants	30	$\frac{1}{8}$ cup	0.262
Supper			
Meat or fish	100	2 slices $2'' \times 2'' \times \frac{1}{4}''$	0.500
Potatoes	100	1 ($2\frac{1}{2}''$ diam)	0.429
Turnips	100	$\frac{5}{8}$ cup	0.338
Tomatoes	100	1, $2\frac{1}{2}''$ diam	0.275
Pineapple	100	$\frac{2}{3}$ cup, diced	0.321
Bread	30	1 slice	0.032
Butter	7	$\frac{1}{2}$ T	0.0009
Milk	200	1 glass	0.286

Totals: Approx P 112, F 110, C 270, Cal 2518 Potassium, 6.0157 Gm

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ENDOCRINOLOGY

BY CHARLES W. DUNN, M.D.

THE POTENCY OF CERTAIN COMMERCIAL HORMONE PREPARATIONS

F. E. D'Amour and M. C. D'Amour¹ report the results in their assay studies of commercially prepared estrogenic, gonadotropic and adrenal cortex hormones, which emphasize the fact these commercial preparations vary greatly in actual biologic potency.

These hormones are of relatively recent development, when compared with epinephrin or insulin, and uniform assay methods have not been adopted for them. nor has the problem of their deterioration been sufficiently studied.

From the estrogenic substances studied the results are as follows: 1. *Hydroxy-ketone-estrin* For this form of estrin, the Health Organization of the League of Nations has adopted an "international standard," which consists of pooled material from a number of laboratories. It has established 0.1 gamma of this material as the "international unit." The commercial preparations were assayed directly against the international standard material, the same method of assay being used for both. It

was found that the oil preparations contained the labelled content, and minor differences between them are probably of no significance. The biologic activity of the aqueous preparations, however, per I. U., stated by the label to be present, was only from one-sixth to one-seventh as great as the biologic activity per I U. of the international standard material.

2. *Tri-hydroxy-estrin* Only 1 preparation was studied, theelol Parke Davis, lot No. 3128030. This was in capsule form and labelled to contain 2000 R. U. or 0.12 mg. of theelol per capsule. The method of assay was not stated. It was found to contain approximately the labelled potency on the basis of the canalization method of assay. However, this unit is very small as compared to the more familiar estrus smear method. The clinician expecting the same response from 2000 "canalization" units as from 2000 "estrus smear" units would be disappointed. It is advocated that manufacturers state the number of units present according to both assay methods.

As no standard method for the assay of gonadotropic substances has been

adopted, the assay method used in the studies was that used by the manufacturer. Ten commercial preparations were assayed, with the results as follows: The urinary and placental preparations contained approximately the labelled number of units, according to the method of assay employed. The pituitary products, on the other hand, contained relatively little or no activity. However, in rating these activities, the method of assay must be taken into account. It requires less material to produce a given reaction in a 30-day-old animal than in a 22-day-old animal. It requires less material to produce an estrus smear than to produce luteinization. In the case of the placental preparation, the "unit" represents the *daily* dose; for the others, the total dose. It is therefore obvious that while the labelled number of units may be present, the actual amount of biologically active substance may vary greatly, depending on whether the unit chosen be large or small. It is advocated that the manufacturers agree on a uniform method of assay in order to avoid the present unfortunate confusion.

Four growth hormone preparations were assayed, using the method of the manufacturer. It was concluded that these preparations contained considerably less than the indicated potency.

In discussing the studies, the authors state they believe the manufacturers of the commercial hormone preparations to be making an **honest and sincere effort** to produce dependable therapeutic agents, and the manufacturers themselves would no doubt be the last to assert that complete success had been achieved.

The authors further state that in the light of the study presented, 2 general criticisms are justified: First, extracts of the anterior lobe, both gonadotropic

and growth, and aqueous estrin preparations, appear to deteriorate on standing, therefore the problem should be studied and if the time during which activity is retained can be determined, it would be well to place the expiration date on the containers. Second, the criticism of lack of uniformity in assay methods and units should be met. Although the Health Organization of the League of Nations has adopted a unit for estrin and will, probably, take official action in regard to other hormones, there is no valid reason for the leading pharmaceutical firms to wait until that time. They should agree now upon uniform methods of assay and upon standard units.

ADMINISTRATION OF HORMONES

An editorial in *The Lancet*² states: The effectiveness of oral endocrine therapy seems to depend upon the chemical complexity of the material administered.

The active principle of the thyroid, probably a tripeptide containing the aminoacids thyroxine and diiodotyrosine and a comparatively simple compound, is easily absorbed by the mucous membrane of the small intestine. In theory the sex hormones, which are sterols, should likewise be absorbable through the alimentary tract, and that this is true of the estrogens may be deduced from the spectacular results obtained with oral estrin therapy in the menopausal syndrome. Estriol is absorbed in larger proportion than estrone when administered in this manner, although it is less potent than when given by injection; but either form may be administered orally, provided the dose (according to various estimates) be from 5 to 30 times greater than the dose prepared for injection. Since progesterone and the androgens are

sterols, they should also be absorbable through the intestine, but they cannot be administered orally in view of the fact they are not technically obtainable in high enough concentrations.

At the moment no convincing evidence indicates other hormones to be effective by mouth, thus oral polyglandular therapy is considered correspondingly valueless. This holds true of the anteriorpituitary preparations (as well as of others), in as much as the confidence of some clinicians in their efficacy is not upheld by animal experimentation.

Posteriorpituitary extract is often prescribed for diabetes insipidus in the form of snuff, thereby avoiding the many unpleasant symptoms arising from frequent injections of large doses. It had been hoped that anteriorlobe hormones could also be absorbed from mucous membranes, but gonadotropic extracts placed in the vagina have in practice not proven effective. On the other hand, estrogens may definitely be given in this way: in fact, vaginal suppositories are sometimes used in the treatment of vaginal lesions associated with ovarian deficiency. Zondek is cited as advocating the application of hormones to the skin in preference to ingestion, because of the possibility of more complete absorption, more especially when an alcoholic tincture is used. This tincture is an improvement on his estrogenic ointment, devised to be applied locally to the breasts in cases of subnormal mammary development. Mammary tissue would appear to be especially sensitive to this form of estrogenic stimulation, from the fact that male employees, packing ampoules of estrogenic material, are very apt to develop tender swelling of the breasts from the continual handling of the estrogenic substances. The success of percutaneous administration has led to the inclusion

of estrogens in cosmetic creams, but these may not be considered to have "skin food" properties, and their continuous application, if they contain a high estrogenic content, may derange the menstrual cycle, if not causing even greater trouble.

Summing up, most endocrine preparations have to be given by injection; and the sterol hormones, because they are soluble in high concentration only in oil, must be injected intramuscularly. From this arises the problem: how to prolong the action of single doses, thereby avoiding frequent injections. The duration of effect has been found to be in direct proportion to the insolubility of the compound in the body fluids. It is this principle which underlies the use of the new insulin compounds, such as zinc protamine insulin. The solubility of the sex hormones may be reduced by administering them in the form of an ester, such as estradiol benzoate or testosterone propionate. This form considerably lengthens the duration of action, hence a constant level of effect may be obtained by twice-weekly injections of the former and weekly injections of the latter. Progesterone is more difficult to esterify and none is as yet available for chemical use, although reports have appeared of an effective oral progesterone ester. Deanesley and Parkes have evolved a method for obtaining far more prolonged action, namely, the subcutaneous implantation of a tablet of compressed crystals of the pure hormone, the active principle being continuously absorbed in small quantities from the surface. This method is now being tested clinically, and Bishop describes its effectiveness in controlling the menopausal symptoms of a young female castrate: A 14 mg. tablet of estrone appeared to be effective for 4 or 5 weeks.

CUTANEOUS ABSORPTION OF SEX HORMONES

C. R. Moore, J. K. Lamar and N. Beck³ report their results in the application of androgens and estrogens in a lanolin-like menstruum or cream to the shaven and unshaven skin of experimental animals, which demonstrate the ready absorbability of the sex hormones through the skin.

The concentration of testosterone and testosterone propionate used was 50 mg. per ounce of cream. The treatment consisted usually in a daily application containing 0.6 mg. of the pure chemical. This dosage, continued for 20 days, resulted in a normal reproductive state in the accessory reproductive organs of castrated males, a precocious stimulation in the development of young males, and a stimulation in the development of adult males to above normal levels. The seminal vesicles of the animals treated with free hormone averaged 50 per cent greater than did those from castrates treated with the propionate. Another series so treated and investigated revealed seminal vesicles 100 mg. heavier than those from males receiving the propionate. It becomes evident, therefore, that testosterone, when applied to the skin, is more effective than testosterone propionate.

Investigations as to the relative value of testosterone applied to the skin and administered subcutaneously in oil revealed the cutaneous application to produce seminal vesicles double the weight of those produced from injection.

These androgens, applied cutaneously, obtain effects similar to those obtained with subcutaneous injections, such as: (1) Maintenance of reproductive accessories in castrate males at all ages; (2) reconstitution of castrated guinea pigs within 7 days of treatment to a state of producing coagulable ejaculates on elec-

trical stimulation of the head, and (3) production of injuries to testes of normal growing young male rats.

Experiments with estrogen in commercial face creams were pursued with approximately 8.2 micrograms of estradiol in lanolin-like base, or one-fifth the amount recommended for daily feminine facial use. The treatment was continued from 2 to 3 days, to 3 weeks, and resulted in: (1) Stimulation of mammary development on normal male guinea pigs—as much as 3- to 5-fold gain in height of the mammary nipples; (2) inducing of cornified vaginal estrous smears in spayed female rats within 2 to 3 days; (3) maintenance of, or increase in, normal growth of the uterus in young or mature spayed rats, and (4) reduction in the weight of testes by 80 per cent and the weight of seminal vesicles by 90 per cent in young male rats in comparison with normal litter mates.

These results suggest not only the efficiency of the cutaneous application of sex hormones in ointment, but emphasize the caution necessary when the method is used by normal persons.

CUTANEOUS APPLICATION OF FOLLICULAR HORMONE

B. Zondek⁴ states the solvent employed is the decisive factor in the greater absorbability through the skin of the estrogenic hormone. The absorption through the skin of the hormone dissolved in oil is one-seventh; dissolved in an organic solvent such as benzol, ether, or 96 per cent alcohol, its absorption is complete. That alcoholic tinctures administered percutaneously have definite therapeutical value has been proven by clinical observation.

This therapy was pursued in 12 cases throughout 18 menstrual cycles, during which period bleeding was induced 10 times. A dose of estrogenic hormone given percutaneously proved equally as effective as the same dose injected subcutaneously. However, in 3 of the 8 failures, subsequent injections of hormone induced menstruation, thereby showing that the percutaneous method of administration is still somewhat inferior to the subcutaneous method.

The percutaneous application of estrogenic hormone, followed by the injection of progesterone, will produce uterine bleeding in primary and secondary amenorrhea. While progesterone is likewise absorbable through the skin, the present high cost of manufacture, together with the greater content necessary for this type of administration, makes the method impractical until the production cost is radically reduced.

FURTHER EXPERIMENTS ON THE ADMINISTRATION OF HORMONES BY THE SUBCUTANEOUS IMPLANTATION OF TABLETS

R. Deanesly and A. S. Parkes⁵ report further experiments with estrone, estradiol, testosterone, and testosterone propionate administered by the subcutaneous implantation of tablets, together with some preliminary experiments with progesterone and diethylstilbestrol.

The tablets were inserted into the experimental animal through a slit in the skin into the subcutaneous tissue. No signs of local reactions were subsequently observed. The tablets were easily recoverable by operation, or at autopsy, and were dried and reweighed. The tablets were mostly dish-shaped, but a few were angular pieces, and in all

cases the mass remained hard and compact after several months' implantation.

Most of the estrone and estradiol tablets used weighed between 5 and 20 mg. The rest, made in a hand machine, weighed 80 to 100 mg. Testosterone and testosterone propionate weighed about 100 mg.

It was found that in the rat estradiol is absorbed nearly twice as fast as estrone, hence it may be a preferable substance where intense dosage is required. The rate of absorption of testosterone is as previously reported, and is undoubtedly absorbed much faster than estrone and somewhat faster than testosterone propionate. The rate of absorption of estrone in tablets up to 100 mg. is between $2\frac{1}{2}$ and 10 per cent per month, that of testosterone propionate about 15 per cent per month, and that of testosterone about 25 per cent per month. The absorption of progesterone in small tablets appears to be comparatively rapid, and that of diethylstilbestrol more rapid than estrone.

Apparently the rate of absorption from a tablet depends largely on its surface area, hence the absorption is much greater, though proportionately less, from a large tablet than from a small one. It is therefore evident that implantation of very large tablets of estrone is not an advisable means for intensifying the dosage, as the duration of action is also much prolonged, hence it is wiser to intensify the action by inserting a number of tablets of a size calculated to last for the desired period: *e.g.*, a 10 mg. tablet, lasting a year, would average some 2000 I. U. weekly, thus 20 such tablets, implanted simultaneously, would average 40,000 I. U. over a year or more which could not be obtained with 1 tablet of 200 mg.

The technic appears of value in maintaining a long and steady effect in the

depression of the gonad-stimulating and growth-promoting activity of the pituitary by estrogens, and in the masculinization of the female by androgens. One administration of hormone by tablet implantations enables a treatment of long duration

ACTION OF THE SYNTHETIC ESTROGENIC SUBSTANCE, DIETHYLSTILBESTROL⁶

Diethylstilbestrol, a synthetic estrogenic substance, has an action similar to estrone on the uterus of ovariectomized rats, on the mating reaction, vagina, and uterus of immature rats, on the uterus of immature rabbits, and on the feathers of capons.

The substance is approximately $2\frac{1}{2}$ times as active as estrone, as ascertained by the vaginal-smear method. It has, however, appreciably less stimulating action on the mammary tissue than estrone.

THE ADRENALS

Adrenal Insufficiency⁷

Diagnosis—When all other means of diagnosis have been impossible, the use of a new modified salt-poor diet test for the diagnosis of adrenal insufficiency is advocated. A test, based on the observation that potassium salts administered to a patient with Addison's disease will cause a much increased output of sodium and chlorine in the urine, is as follows:

The patient is placed on a diet low in salt, the daily intake being 0.59 Gm sodium and 4.1 Gm potassium. Potassium citrate, in dose equivalent to 33 mg of potassium per kg. of body weight, is given on the first and second days, and the urine is collected for 4 hours on the morning of the third day, 20 cc of fluid per kg of body weight being adminis-

tered before 11 A. M. At the end of the test an immediate therapeutic intravenous injection of 1 liter, containing 50 Gm glucose, 10 Gm sodium chloride, 5 Gm. sodium acetate, and 20 cc of active cortical extract, is given.

Under this regimen considerable overlapping was found in the serum concentration of sodium, chlorine, potassium, and urea in normals and in Addison's disease patients, but there was a clear-cut distinction in the concentrations of sodium and chlorine in the urine, irrespective of the levels in the serum. The sodium concentration in the urine of the Addison's disease patients had a mean value of 207 mg per 100 cc (165-282) as against the control patients' 224 mg per 100 cc., and, correspondingly, the chlorine values were 293 mg per 100 cc (229-356) as against 54 mg per 100 cc.

The test permits an easy determination of the chlorine concentration in the urine, and, moreover, is available even when there is no great fall in the serum chloride.

Diagnostic Significance of Concentrations of Chloride, Sodium and Potassium in Urine and Blood—H. H.

Cutler, M. H. Power, and R. M. Wilder⁸ present a diagnostic procedure in Addison's disease which entails less risk of collapse in the patient, requires less time to complete and is equally as informative as the 6-day diagnostic period of restricted salt-intake hitherto employed.

The diagnostic procedure was studied with 35 subjects, 7 of whom had Addison's disease. The medication which the latter were receiving, such as adrenal cortex extract or extra salts of sodium, was withheld for 1 day prior to the day of examination. A longer period proved unnecessary.

The standardized procedure was as follows: *First day.* A diet low in salt providing 0.95 Gm of chloride ion, 0.59 Gm of sodium and 4.1 Gm. of potassium.

The fluid intake was not measured this day, but the free drinking of water was encouraged. During the afternoon extra potassium was given, the dosage being 33 mg. per kg. of body weight of potassium citrate (42 mg. potassium citrate per pound). *Second day.* The fluid intake was made to equal 40 cc per kg. of body weight. The dose of potassium citrate was repeated in the morning. *Third day.* Twenty cubic centimeters of liquid per kg. of body weight was given before 11 A M. At noon the examination ended, except when additional evidence of the state of adrenocortical function was desired, in which case the examination was extended. All cases in which adrenal insufficiency was suspected received at the end of the examination an intravenous injection of 1000 cc of sterile solution, containing 50 Gm. of *d*-glucose, 10 Gm. of sodium chloride, 5 Gm. of sodium citrate and 20 cc of an active preparation of cortical hormone.

Blood was taken from the cubital vein at 8 A M. on the *second day*, and at 10 A M. on the *third day*. Urine was collected in 3 periods. *Second day*, from 8 A M. to 8 P M., during the night from 8 P M. to 8 A M., *third day*, from 8 A M. to 12 noon.

The blood plasma sodium average value in subjects with Addison's disease was distinctly lower than that of all other subjects. However, the former group's range of values widely overlapped that of the other subjects. This was as true for the third day as for the second. The average depression of these values, from the second to third day, in subjects with Addison's disease was 19.4 mg. per 100 cc., that in the other subjects was only 3.6 mg. Again, wide overlapping was evident. These statements apply with almost equal force to the blood plasma chloride values.

The blood plasma potassium average value was only slightly higher in the patients with Addison's disease (about 3 mg. per 100 cc.) than in the other subjects. The values for the 2 groups again overlapped widely.

The range of values in the patients with Addison's disease both for hematocrit determinations and for blood urea extended far into the zone of values found in normal subjects.

Determinations for urine sodium, based on the 24-hour urine collection of the second day in terms of mg. of sodium per kg. of body weight per hour, revealed the patients with Addison's disease had a mean value in excretion more than 3 times as great as that of the other subjects; and based on the third day's 4-hour collection, the mean value was more than 5 times as great. In this 4-hour collection the mean for the subjects with Addison's disease was 206.7 mg. per 100 cc., range 165 to 282, whereas the mean for all other subjects was only 22.4 mg., range 6 to 85.

The above statements apply also to the urine chloride. Of greatest significance was the concentration (mg. per 100 cc.) in the third day's 4-hour collection, wherein there was again no overlapping of values between the 2 groups. In this specimen the mean value for subjects with Addison's disease was 293.4 mg., range 229 to 356, and that of the controls was 54.2 mg., range 17 to 141. This tendency of patients with Addison's disease to excrete urine containing chloride in high concentration becomes even more apparent on considering the concentrations of chloride and sodium in their blood were usually depressed.

The excretion of potassium was slightly less in the subjects with Addison's disease, although there was much overlapping in the individual values of the group.

The average volume of the urine in the group of subjects with Addison's disease

was significantly smaller than that of the group of controls. The difference was greatest in the third day's 4-hour period. There was considerable overlapping in values even for this specimen.

Diagnostically, the most significant factor was the concentration of chloride in the third day's morning urine. It was more significant than the volume of urine, the concentration of potassium in the urine, the total amount of chloride, sodium or potassium in the urine, or the values or change in values of the chloride, sodium or potassium in the blood.

The diagnostic procedure is favored because it subjects the patient to less risk of collapse, the concentration of the chlorides in the urine gives as important information as that of sodium and the determination of urinary chloride can be made in most clinics and hospitals.

Synthetic Desoxycorticosterone Acetate in Addison's Disease—S. Levy Simpson⁹ reports a synthetic product, desoxycorticosterone acetate, approximating in chemical formula to corticosterone, was administered to 2 cases of Addison's disease, the first case, with severe adrenal insufficiency, gave an equivocal response, but the second case undoubtedly derived far greater benefit from it than from cortin (5 cc.) dosage).

Biological tests suggested 6 mg. of desoxycorticosterone to be equivalent to 75 to 150 cc. of cortical extract (cortin). From the cases reported it appears that 6 mg. of the substance is equivalent to more than 5 cc. but less than 20 cc. of cortin.

The first case, a woman aged 42, apparently had a progressive lesion of the adrenal glands, since her early requirements of 5 cc. of cortin daily had gradually necessitated being increased to 20 cc. daily. The first dosage of desoxycorticosterone was 3 mg. (0.5 cc.), at early evaluation equivalent to 30 cc. of cortin.

This had to be increased to 12 mg. daily in 2 doses. While her general condition was reasonably good, still the impression was that while desoxycorticosterone acted much more rapidly than cortin its reaction was of shorter duration, the maximum effect wearing off in a few hours. As a consequence the patient was replaced on the daily dose of 20 cc. of cortin in conjunction with a salt mixture, which has maintained her in good health. While the 6 mg. of desoxycorticosterone did not appear so efficacious as 20 cc. of cortin, it nevertheless sufficed to prevent the blood chemistry from showing any gross change.

The second case was a man aged 24. He maintained fair health for some time on 12 Gm. of salt daily with 5 cc. of cortin every other day, but when this no longer proved sufficient, the cortin was increased to 5 cc. daily and resulted in immediate improvement. This therapy was replaced by 6 mg. (1 cc. solution in oil) of desoxycorticosterone, and an immediate gain in strength and well-being was noted, together with a 14-pound gain in weight in as many days. Thus the 6 mg. of desoxycorticosterone appeared to produce far greater effect than did the 5 cc. of cortin, and it also apparently provided complete replacement therapy when used in conjunction with salt.

Enteric Fever

Treatment with Suprarenal Cortex Extract and Vitamin C Intravenously—Najib-Allah¹⁰ reports the therapy and its results in 15 cases of enteric fever (7 typhoid, 8 paratyphoid), of which only 1 failed to respond immediately, and in 3 cases of acute bacillus coli, who showed similar excellent and immediate response.

On laboratory confirmation of the diagnosis, the therapy instituted was as follows: Intravenous injections of supra-

renal cortex extract, in doses between 5 and 20 cc., according to the age and state of the patient, with 500 to 1000 mg. of vitamin C. The usual daily dose of the cortical hormone injected at a time was 10 cc. The 2 products were mixed in the same syringe, as they seem to be more active when injected together. During the same day 2 or more doses of 500 mg. of vitamin C were injected at 4-hour intervals. The cortical hormone was administered with vitamin C for 5 to 12 days, and was followed by 2 intravenous injections daily of 500 mg. of vitamin C alone, for at least 7 days.

The injections produced no pain, shock, or reaction. The effect was dramatic from the first injection. There was abundant urination and a gradual fall of temperature to normal between the third and seventh day. The symptoms disappeared rapidly, and the patients were quickly able to take nourishment. The 1 case, in whom vomiting persisted, received subcutaneously glucose saline, which produced the desired result.

The author recalls that suprarenal cortex extract will increase the bactericidal power of the blood of rabbits, and the combined use of the extract and vitamin C has proved efficacious in protecting guinea pigs from diphtheria toxin. He also points out that in typhoid this combination of cortical hormone and vitamin C favorably affects not only the deficient adrenals in particular but also the whole system. Yet how these changes take place he is unable to explain.

Marasmus

Treatment by Injection of an Extract of Adrenal Cortex—W. A. Hislop¹¹ reports his results with adrenal cortex extract (eucortone) in marasmus, and the consequent reduction in the death rate from the disease of 41 per cent. from 55 to 14 per cent.

A first series of 5 cases received insufficient dosage, yet the results strongly suggest the adrenal hypofunction was at least in part being corrected. The weight gain was far more rapid during the administration of eucortone than in the previous period.

A second series of 14 cases received intramuscularly 1 minim per 2 pounds of body weight of eucortone daily. This therapy was continued only 14 days, then suspended for 10 to 14 days, recommenced and continued for 6 to 10 weeks. Of the 14 patients, 11 responded satisfactorily and made good progress, 1 was suffering from otitis media, 1 died after making no response, and 1 left hospital improved after having shown no definite response.

The clinical and biochemical picture suggests some connection between marasmus and adrenal insufficiency, but this does not necessarily mean all cases of marasmus to be due to an adrenal insufficiency. Rather, says the author, whatever the original cause, there is ultimately an adrenal hypofunction which must be corrected for recovery to proceed. If the administration of adrenal cortical extract could tide over the period of adrenal insufficiency, so enabling the system to utilize adequate nourishment, a re-establishment of function would be followed by an approach to normal health. The treatment thereby becomes of therapeutic value.

THE PARATHYROIDS

Generalized Osteitis Fibrosa

Retroesophageal Parathyroid Tumor as a Cause—E. N. Allott and J. Jemson¹² present the case of a girl, aged 19, with a retroesophageal parathyroid tumor. The patient had felt quite well up to the year previous to examination, but at this time the end of the

right clavicle became noticeably prominent. Then pain and numbness in the right arm and the gradual loss of its use took place. A reconstruction of the sternoclavicular joint had later been performed at another hospital, following which the patient developed severe pains in both arms and legs. She noticed a slight tenderness in the bones. The increasing pain, together with muscular weakness, made her unable to walk properly.

Nine months following this first operation she had developed a pain on the left side of the chest which was aggravated by coughing. There was also poor appetite and constipation, but otherwise no symptoms referable to other systems.

The examination showed a pallid, sallow complexioned girl who was not able to stand alone. Although the chest revealed no definite physical signs, there was a slight lagging of the left side on breathing. Muscular power was generally very poor; she could barely lift her legs off the bed. Her bones were slightly tender on palpation, but there was no abnormal physical signs. The urine was normal.

The x-rays revealed several small rarefied areas in the ribs on the left side, rather thin clavicles, and a ragged appearance at the outer end of the right clavicle. The lungs were negative. Further x-rays showed a general decalcification. The skull showed general mottled decalcification, with several larger areas of rarefaction. The pelvis, funnel-shaped, showed general rarefaction. Large cyst-like areas were in the iliac bones and pubis, and irregular and delayed union at the epiphyseal junctions of both ascending rami. Both humeri showed general mottled decalcification, with thinning of the cortex. The radius and ulna on the right side showed large rarefied areas just above the wrist. The fourth and

fifth metacarpals on both sides showed cyst-like rarefaction. The leg bones, especially the tibiae, showed severe decalcification, but no cysts were seen.

The blood studies gave the typical high serum calcium and plasma phosphatase content, with a low serum inorganic phosphate. A pronounced negative calcium balance was determined.

The surgeon, failing to find the parathyroid at its usual site, explored behind the esophagus. The tumor was found in the midline immediately in front of the last cervical and first dorsal vertebrae. It was connected to the posterolateral aspect of the thyroid by a fine pedicle consisting of 2 small veins, a small artery, and a few strands of connective tissue. A small piece of the thyroid was removed with the tumor. The pathological report revealed an adenomatous hyperplasia of the parathyroid.

The day following the operation the patient complained of stiffness of the face and tingling in the limbs. Tetanic symptoms persisted for about 10 days after the operation. Convalescence was untowardly delayed, but 18 days postoperatively she was able to walk with assistance, and to walk alone after 25 days. Six weeks following the operation she still complained of some pain on walking, but her general condition was greatly improved. The pains gradually disappeared, and 1 year later she was completely well.

Prior to the operation, the calcium and phosphorous balances were markedly negative. A month after operation the retention of calcium was very good, and 9 months later the calcium and phosphorous balances were normal.

Blood Studies — Preoperatively, the serum calcium was 15.5, rising on the day of operation to 17.3. First day postoperative this dropped to 11.3, and 3 days later to 8.7 mg. It remained at 9.5 mg per 100 cc of blood. The plasma phos-

phatase was very high, at 1.1 unit per cc., and was still above normal, 0.5 unit per cc., 9 months after the operation. The serum inorganic phosphate was low throughout. An extremely low value of 1.1 mg. was observed on the first post-operative day, but it did rise once, post-operatively, to 3.4 mg. per 100 cc. of blood.

Hyperparathyroidism

Idiopathic Hypertrophy (Hyperplasia?) of Parathyroid Tissue as a Cause—There first appeared a paper on this subject in 1934, wherein was contained the report of 3 of a series of 19 cases exhibiting this condition, in which the diagnosis was proved by operation and the pathologic examination revealed a then-called diffuse hyperplasia of all parathyroid tissue, rather than one or more circumscribed adenomas. At that time it was pointed out these cases represented a separate disease entity. Subsequently there has been a total of 35 proved cases of hyperparathyroidism, 6 of which have been cases of "hyperplasia." This is a unique group, inasmuch as in apparently no other clinic has a diagnosis of this condition been made during life.

F. Albright, H. W. Sulkowitch and F. Bloomberg¹³ report a follow-up of the 6 cases of "hyperplasia," in which the histologic picture of the parathyroid glands is entirely different from that seen in cases of compensatory hyperplasia of parathyroid tissue, *i. e.*, "compensatory hyperplasia" meaning the condition encountered where an increase of the hormone is necessary to maintain the serum calcium level at a normal value, and the "idiopathic hyperplasia" meaning the condition where some influence is apparently driving the parathyroid tissue to produce more hormone than is required, with resultant hypercalcemia and all the sequelae of primary hyperparathyroidism.

In discussing the cases, the authors admit the question has not been definitely settled whether the enlargement of the glands is due to hyperplasia and hypertrophy, or just to hypertrophy of the cells. In the 6 cases the weight of the actual tissue mass ranged from 19,100 to 2510 mg., roughly 100 to 30 times normal. The diameters of the individual cells were approximately 3 to 4 times normal size. Hypertrophy of the cells can, if not entirely, at least in large part, explain the increase in size. The fact the histologic appearance is entirely different from that seen in conditions of known hyperplasia is further evidence that hyperplasia may be playing a subordinate rôle.

In studying sections of the tissue, the parathyroid disturbance seems to be one of "all or none." That the condition, once established, remains indefinitely is made clear by the data of 1 case. Thus the underlying abnormality may be assumed to be chronic with, apparently, a distinct correlation between the weight of the parathyroid tissue and the degree of hyperparathyroidism.

It is now fairly safe to say the condition is amenable to permanent surgical cure. The removal of tissue should be such as to leave about 200 mg. In all cases but 1, in whom there is possibility of a fourth gland, the removal of all but 400 mg. was followed by cure. There is no data to say whether the leaving of 1000 mg., for example, will be attended by cure. This is an important question, as the more that can be left in without causing recurrence, the safer the operation will be and the less a subsidence of the so-called hyperplastic state is to be feared. It is important also that the amount of parathyroid tissue left in place be increased if renal insufficiency or marked osseous disease is present.

The cause of the pathologic condition remains completely obscure. No con-

firmatory evidence has been found for the early suggestion the condition might be secondary to an excess of pituitary parathyroid tropic substance. Roentgenographic examinations in all cases failed to reveal any evidence of pathological condition of the pituitary body.

Hyperparathyroidism Simulating or Associated with Paget's Disease

A. B. Gutman and W. B. Parsons¹⁴ report 3 proved cases of hyperparathyroidism, 2 presenting sclerotic lesions simulating Paget's disease, of the pelvis in 1 case, of the skull in the other; and the third case apparently associated with Paget's disease of the tibia and skull.

The first case was a woman, aged 51, suffering with intermittent pyuria. She had been well up to about 48 years of age, when she began complaining of weakness, loss of 20 pounds, and pain in the left flank and lower abdomen. The urine was cloudy. At about 50 years of age the left kidney (nephrolithiasis) had been removed, and following this operation her health had improved, although the weakness persisted. Soon, however, "arthritic" pains began to develop in the left hip, lower back and right knee and became progressively worse. The urine again became cloudy. The physical examination at this time was essentially negative, except for a moderately enlarged, nontender right kidney. The urine showed a heavy trace of albumin and many pus cells. Pyelograms revealed a staghorn calculus in the right kidney pelvis with some dilatation of the pelvis and calices. The lower spine and the pelvis appeared normal. The blood nitrogen was 17.5 mg per cent.

The diffuse "arthritic" pain in the knees, back and fingers continued. Diathermy failed to relieve them. X-rays at 52 years of age revealed "a peculiarity of the architecture of the left innominate bone which suggests osteitis deformans." During the next 2 years the diffuse pain, stiffness and difficulty in walking incapacitated her greatly. Somewhat later, a blood analysis revealed hypercalcemia, hypophosphatemia and increased phosphatase activity. The provisional diagnosis was hyperparathyroidism.

At about 55 years of age the patient was obese, pale, and chronically ill in appearance.

There was a definite rounded, nontender dorsal kyphosis. The proximal half of the right tibia was markedly expanded and slightly tender. There were no other significant findings. No palpable tumor was present in the neck. Repeated analyses of the blood showed consistent hypercalcemia, hypophosphatemia and increased phosphatase activity. The x-rays showed a moderate generalized decalcification of the skeleton with typical blurring of the finer bone architecture. There was a large cyst in the proximal portion of the right tibia and a small cystic area in the region of the medial malleolus on that side. The left side of the pelvis presented Paget-like sclerosis and coarse trabeculations. These changes were now more extensive and were associated with obvious cystic involvement. There was no mottling of the skull but two small cysts were present in the occipital region. A calcium determination showed a negative calcium balance.

An exploration for parathyroid tumor was performed, and posterior to the lower pole of the right lobe of the thyroid gland, at about the level of the clavicle, an ovoid, slightly lobulated tumor was found. Histologic study showed it to be an adenoma of the parathyroid gland. The patient's postoperative course was uneventful. No manifest tetany developed. Two months after the operation she was able to resume housework, her strength had improved but there was still some pain in the right knee. One year after operation she was in excellent condition and very active.

The serum calcium and inorganic phosphorus returned to normal levels within 3 weeks after operation and have remained normal. The phosphatase activity did not decrease until some months after operation, which was slower than in most cases. X-rays taken 5 months after operation showed only slight recalcification, but at the end of a year there was a definite general increase in bone density, much of the "ground-glass" appearance having disappeared. The cystic areas of the left side of the pelvis had become largely sclerosed, with striking diffuse increase of density but without bundling of the trabeculae. The small cysts in the occipital region of the skull were partially sclerotic. Early but definite sclerosis of the large cyst of the right tibia had developed.

The second case was a woman, aged 54, with hyperparathyroidism. She had been apparently well until the age of 41 years, when a fall, which fractured the left femur which had delayed union, had confined her to bed.

ever since. At that time, x-rays of the bones showed decalcification and the diagnosis was "osteomalacia." Her course within the next 13 years was characterized by the repeated occurrence of pathologic fractures of the legs, arms, and ribs; and by the development of extreme deformities, particularly of the legs. Early blood studies showed hypercalcemia, but the inorganic phosphorus to be within normal limits. Later studies showed hypercalcemia and hypophosphatemia, but the phosphatase activity within normal limits.

By 54 years of age, the patient presented the extreme deformities seen in advanced hyperparathyroidism. The legs were atrophied, shapeless, deformed appendages. The pelvis was tilted to the left and distorted. There were bony deformities of both arms. A rounded dorsal kyphosis of the spine was present. The sternum was thrust forward. The skull was enlarged, somewhat resembling Paget's disease. Pronounced prognathism was present without evidences of bony tumor of the jaws. She had no pain when she remained absolutely quiet, but there was some tenderness over the ribs, spine and arms, and the legs were extremely tender to pressure. A nodular mass was palpable in the neck on the left. Blood studies revealed hypercalcemia and hypophosphatemia, but normal serum phosphatase activity. X-rays showed generalized decalcification of extreme degree, particularly in the bones of the legs, in which numerous cysts were present. Cysts were also found in the deformed and decalcified pelvis, and in the ribs. The vertebrae presented a marked "ground-glass" appearance. These skeletal changes were regarded as typical of advanced hyperparathyroidism. The cranial vault, on the other hand, was definitely thickened and diffusely sclerotic. The "cotton-wool" appearance characteristic of Paget's disease was absent, however.

Exploration revealed a tumor inferior to the left lower pole of the thyroid gland, and extending below the manubrium. The mass proved to be a parathyroid adenoma. Following the operation the serum calcium fell rapidly. Tetany did not become manifest. Following the operation the patient gained weight and strength and is now able to get about in a wheel chair.

The third case was a woman, aged 48, desirous of being treated for obesity. Physical examination revealed marked anterolateral bowing of the right tibia, with slight tenderness. At 38 years of age she had developed

pain in the lower back and right knee which was aggravated by exercise. Progressive bowing of the right tibia was noted, with limp and increasing difficulty in gait developing after 5 years. There had been no fractures, no renal colic.

The x-rays taken at the same time as the examination showed marked anterolateral bowing of the right tibia, with thickening of the cortex and coarse, irregular trabeculations. Areas of decreased density were also thought to be present in the mid-third of the shaft. The film was interpreted as either *ostitis fibrosa cystica* or Paget's disease. The serum calcium was normal.

X-rays done the following year revealed the skull to have numerous ill-defined rounded shadows of increased density involving most of the calvarium. There was also some thickening of the floor of the anterior fossa. The changes were regarded (and still are) as typical of Paget's disease. In addition, there was in the occipital region an area of osteoporosis circumscripta, a condition commonly associated with Paget's disease. The diagnosis was Paget's disease. Radiotherapy to the right tibia and skull gave no relief.

At 52 years of age a blood study revealed an unexpected hypercalcemia and hypophosphatemia, with a rise in serum phosphatase activity. This suggested hyperparathyroidism rather than Paget's disease. Repeated x-rays failed to disclose any generalized decalcification or cystic changes. However, the characteristic "cotton-wool" appearance of the skull did not resemble the fine, gramy mottling usually seen in hyperparathyroidism. The area of *osteoporosis circumscripta* was now almost completely replaced by sclerotic bone.

At 54 years of age she was obese, and was free of acute pain only when she remained in bed. The severe occipital headaches had recurred. Except for obesity the physical examination was negative. There was hypercalcemia, hypophosphatemia, and increased serum phosphatase activity. A calcium determination revealed a marked negative balance. This disclosure, typical of hyperparathyroidism, is inconsistent with the normal calcium balances found in uncomplicated Paget's disease.

Exploration for parathyroid tumor was performed, and, at the site of the left superior parathyroid gland, a tumor was found and removed. The mass proved to be a very vascular parathyroid adenoma. The postoperative course was uneventful. Slight symptoms of

tetany were easily controlled by calcium administration. The patient improved in some respects after the operation, but the general result after 8 months is unsatisfactory. The pain in the arms disappeared, only to return. The pains in both knees, hips, and back are unimproved. X-rays 3 months following operation reveal no change. The calcium and inorganic phosphorous contents of the serum have remained normal. The postoperative phosphatase activity of the serum has shown no definite decline 6 months following removal of the tumor.

In summary, Case 1 appears to be an instance of hyperparathyroidism simulating certain roentgenologic aspects of Paget's disease. The atypical, localized bone condensation simulating Paget's disease may well be the result of an earlier transitory, spontaneous remission in the course of parathyroidism.

Case 2 showed typical advanced hyperparathyroidism, yet an apparently discrepant finding was the enlargement of the skull with definite thickening and sclerosis of the cranial tables, superficially resembling that seen in some cases of Paget's disease. The absence of "cotton-wool" lesions in the skull and of any increase in serum phosphatase activity argue against the presence of Paget's disease. It is felt the case is an instance of advanced generalized *osteitis fibrosa cystica* with only moderately overactive parathyroid function when operated on, and presenting spontaneous recalcification of the skull simulating Paget's disease superficially.

Case 3 showed the clinical symptoms and signs of Paget's disease which were not incompatible with hyperparathyroidism, the x-rays were typical of *osteitis deformans*, and the blood analyses and markedly negative calcium balance indicated parathyroid overactivity. Yet the interpretation of the case, it is felt, would be as an instance of hyperparathyroidism associated with Paget's disease. Whether

or not the presence of Paget's disease in this case precipitated the development of hyperparathyroidism (or *vice versa*) is speculative. This seems unlikely, however, in view of the evidence pointing to the 2 conditions being discrete and unrelated entities. These cases are felt not to be incompatible with this latter assumption.

Parathyroid Tetany

Treatment with Dihydratichysterol—C. M. MacBryd¹⁵ reports his results in 7 cases of chronic parathyroid tetany (6 with chronic hypoparathyroidism following thyroidectomy and 1 with idiopathic tetany) treated with dihydratichysterol, which maintained the patients free of symptoms of hypocalcemic tetany, and raised and retained their serum calcium at normal levels.

The 7 patients were white women, aged 21 to 56. The first case, aged 43, had had 2 thyroid operations over a 20-year period. Almost immediately following the second she had developed numbness and muscular spasms. A *parathyroid transplant* later gave temporary improvement, then *parathyroid extract* was administered until a tolerance developed. After a prolonged period of 6 mg of *calcium lactate* and 20 drops of *viosterol* twice daily, followed by 2 weeks of no viosterol and 10 Gm. daily of the calcium, the serum calcium ranged from 5.6 to 6.5 mg. and the blood phosphorous from 4.7 to 6.2 mg. per 100 cc. *Dihydratichysterol* therapy was then instituted. One-third cubic centimeter was given thrice daily and the same calcium intake maintained. At the end of 6 days the serum calcium had risen to 7 mg. per 100 cc., and by the tenth day had reached 10.1 mg. The dose was reduced to 1/3 cc. daily, and on the twenty-second day the serum calcium was 10.6 mg. The blood phosphorous fell to 3.6 to 5 mg. per 100 cc. During 7 months the therapy has

been calcium lactate, 2.5 Gm. 4 times daily, and dihydrotachysterol, $\frac{1}{3}$ cc. daily, which has maintained the patient symptom-free and her serum calcium at approximately normal levels.

The second case, aged 35, had had 2 thyroid operations, roentgen therapy, and a third thyroid operation within a 7-year period. Following the last operation she developed severe symptoms of tetany, and the serum calcium dropped to 6 mg. per 100 cc. Calcium gluconate and viosterol failed to control the symptoms, and while subsequent administration of *parathyroid extract* completely relieved the symptoms, a tolerance developed. Despite doses of 200 to 400 units daily, the blood calcium remained at about 6 mg., and there were severe muscular contractions. Parathyroid transplants were tried 4 times, but no definite improvement was noted therefrom. When calcium gluconate, viosterol and diluted hydrochloric acid failed to change the serum calcium of 7 mg., dihydrotachysterol was administered, the dosage being 0.5 cc. daily. Within 4 days the blood calcium had risen to 8.9 mg., and the calcium gluconate was reduced from 20 to 3 mg. daily. On this dosage, the blood calcium rose to 10 to 10.2 mg. When the dihydrotachysterol dose was reduced to 0.25 cc. daily, the blood calcium slowly fell, until at the end of 9 days it had reached 8.2 per 100 cc. A 2 mg. increase in the daily dosage (total 5 mg. daily) caused the serum calcium to return to its previous high of 10.2 mg. For over a year the therapy continued has been 0.25 cc. of dihydrotachysterol and 5 to 8 Gm. calcium lactate daily, which has resulted in maintenance of the blood calcium at approximately normal levels and relief of all the patient's symptoms.

The other 5 cases responded similarly to the therapy. The general therapeutic dosage has been 1 cc. daily of dihydro-

tachysterol, but the range has been from 0.5 to 6 cc. daily, although the latter high was held for only 2 days. The maintenance dosage has ranged from 0.25 to 1 cc. daily, the average being $\frac{1}{3}$ cc. daily. The calcium gluconate or calcium lactate dosage has ranged from 4 to 10 Gm. daily.

It is evident that the serum calcium can be raised to normal with dihydrotachysterol alone, but if no calcium is added in the diet in conjunction with it, then 1 to 2 cc. daily is necessary. The rise in serum calcium with parathyroid extract is usually apparent in a few hours, reaches a maximum within 3 to 8 hours, then disappears within 24 to 48 hours. With dihydrotachysterol the rise is first noted in about 48 hours. With small doses the rise continues, so that within 7 to 14 days normal calcium levels are reached. Thereafter the dose may be considerably decreased and the normal level still maintained. The blood phosphorus generally shows an initial rise, followed by a slow fall as the calcium reaches normal levels. If dihydrotachysterol therapy is discontinued, the blood calcium will slowly return to the previous low levels in from 1 to 3 weeks. Large doses are dangerous as they may cause hypercalcemia.

The advantages of dihydrotachysterol over parathyroid extract in the treatment of chronic tetany are as follows: (a) The effect is more prolonged, (b) it is taken orally, (c) no tolerance is developed, (d) it is less expensive, and (e) it is stable and retains its potency when kept at ordinary room temperature.

Again it is stressed that extremely careful attention be given to the dosage, not only because of the drug's potency, but because of the great variation in individual tolerance to it. Frequent blood calcium determinations should be made until maintenance therapy is achieved.

THE PITUITARY

Pituitary Emaciation (von Bergmann)

R. H. Kunstader¹⁶ discusses Simmonds' disease and von Bergmann's *pituitary magersucht*, and reports 2 cases of young women with a syndrome resembling the latter

The author reviews, "In 1914, Simmonds described the syndrome of cachexia hypophyseopriva due to destruction of the anterior lobe of the hypophysis, characterized by progressive cachexia, precocious senility, dental caries, low basal metabolic rate, decrease in size of the vital organs (splanchnomicria), loss of pubic and axillary hair, and loss of libido and sexual function. With few exceptions, the disease is confined to adults and almost invariably progresses to a fatal outcome. Only 5 cases have been reported in children and only 1 was verified at autopsy. Four of the 5 showed improvement with glandular therapy (one received supplementary roentgen irradiation) "

Several female children with marked emaciation resulting from a progressive loss of weight and with a concomitant suppression or retardation of sexual development have been under his observation for 2 years. They were apparently illustrative of the early stages of Simmonds' disease, yet they differed by reason of their greater youth, their absence of severe cachexia, and, of prime importance, their ability to respond favorably to endocrine therapy. In discussing the syndrome presented by these young girls, the author says, "It is conceivable that a suppression of the anterior lobe may occur as a result of congenital defect, a toxic influence secondary to the infectious diseases of childhood, or it may be due to a functional exhaustion resulting

from the added strain of puberty, or a combination of any of these factors "

That a marked clinical difference existed between thinness (*magerkeit*) and the disposition toward emaciation (*magersucht*) was probably first realized by von Bergmann. He it was who believed *magersucht* a clinical entity to be differentiated from the emaciation due to carcinoma, tuberculosis and other chronic diseases, stressing, furthermore, that all too little consideration was given to the underlying cause of such a diagnosis as anorexia and thinness associated with emotional and psychic changes.

The more recent information relative to the physiology of the hypophysis reveals it as the dominant power of the endocrine machine, whose removal or destruction results in atrophy of the gonads, thyroid and adrenals, which is illustrated clinically in Simmonds' disease. Emaciation then becomes a consequence of a disturbance in fat and carbohydrate metabolism that has resulted, in turn, from the altered secretion of fat metabolism, adrenotropic, diabetogenic, and thyrotropic hormones of the anterior lobe. The depressed or delayed sexual function is attendant on the insufficiency of pituitary gonadotropic hormone. The lowered B. M. R. and hypotension likewise are attendant on the secondary changes in the thyroid and adrenals.

The author questions whether several reported cases of Simmonds' disease having recovery were actually Simmonds' disease or *von Bergmann's magersucht*, since in von Bergmann's words "only those cases should be called Simmonds' cachexia which can be verified anatomically." Despite the confusion on the etiology and pathogenesis of *magersucht*, several authors have agreed that etiologically in certain cases the pituitary is the most important endocrine organ.

Pituitary magersucht is rarely seen in the male; there was only 1 in the 15 cases reported by von Bergmann, and only 2 in the 15 cases reported by Bickel. In the female it is seen at puberty, during adolescence or following pregnancy. The symptoms are a loss of weight progressively slowly to emaciation over a few months to several years' time, in conjunction with which there is weakness, fatigue and anemia (the anemia being frequently and erroneously given as the cause instead of as the effect). Although the mental faculties remain alert, there are often psychic and nervous symptoms. In contrast to Simmonds' disease, there is no falling of hair and nails, no marked dental caries, no somnolence or cachexia. There is almost always a gradual development of amenorrhea in the older girl or, in the younger, failure of the menstrual cycle to establish itself. In Robin's belief, the fact the amenorrhea in the older girl is present anterior to the anorexia is of significance in explaining the pituitary origin of the disease. Von Bergmann advises that the tall, thin, asthenic girl with chronic anorexia, psychic disturbances and amenorrhea be watched, just as should be watched the vagotonic individual for hyperthyroidism.

Thus, emaciation, retarded sexual development, delayed secondary sexual characteristics or hypogonitism, and visceroptosis are the outstanding physical signs, and hypotension, a low B M R and low fasting blood sugar are characteristics. In addition to the low blood pressure, the pulse is frequently slowed, but there are no signs of increased intracranial pressure. The heart may be of the "drop" or asthenic variety and smaller than normal. Roentgenograms reveal small sella, as demonstrated in the 4 cases described by Dogliotti. There is no distortion or erosion of the ethmoid processes.

Very often there are complaints of vague epigastric pains usually following meals. Gastric analysis varies; in some cases there is hypochlorhydria, and in others hyperchlorhydria. There is very often an increased tolerance for sweets; however, von Bergmann has described a particular dextrose tolerance curve wherein there is a normal rise (differing from the diabetic) but a retarded fall over the 3-hour period. The response to insulin is more severe and prolonged than in the normal individual, which probably can be explained by a decreased secretion of anterior pituitary insulin antagonizing hormone. Because of the increased sensitivity to insulin, its use is not recommended for treatment.

There is no pituitary gonadotropic hormone or estrin demonstrable in the urine, which indicates a primary and secondary gonadal insufficiency. Merklen, Aron, Israel and Jacob describe an "histologic test for hypofunction of the hypophysis in certain cases of emaciation," which consists of injecting 5 cc. of fresh urine from the patient on 3 consecutive days into a female rabbit 3 weeks of age and weighing 160 to 200 Gm. The rabbit is then killed and the thyroid and ovaries examined histologically. Normally, there is a slight increase in activity of the thyroid and ovaries. In hyperpituitarism there is evidence of an excessive stimulation of the thyroid and ovaries and conversely, in hypopituitarism no reaction in either organ. Their tests in 15 cases of pituitary emaciation showed 14 subnormal reactions.

Diagnosis—The diagnosis of pituitary emaciation should be made only after a careful study, and elimination of all other possible causes for the disease. The author points out the symptoms and signs of Simmonds' and Addison's diseases as follows: "Simmonds' disease has a tendency to occur in older individuals; the

course is progressively downhill and usually terminates fatally. The emaciation develops into a severe cachexia with muscular atrophy. Fatigue and exhaustion are severe, somnolence develops, the skin becomes dry and wrinkled, the nails fall, and the teeth decay. Premature senility usually develops. Roentgenographic examination may reveal changes in the region of the sella indicative of a tumor. Response to replacement endocrine therapy is temporary. Addison's disease occurs usually in the adult. In addition to asthenia and hypotension there is a characteristic pigmentation of the skin and buccal mucosa, and severe gastrointestinal disturbances. Frequently there is evidence of a tuberculous or syphilitic infection."

Further, "careful clinical and laboratory examinations should exclude tuberculosis, malignancy, chronic gastrointestinal disease, blood dyscrasias, hyperthyroidism and diabetes. Psychogenic and neurogenic disturbances must be carefully eliminated, in view of the fact they frequently occur during puberty and adolescence."

Treatment—"The principles of treatment consist primarily in the activation of the gonads by the *anterior pituitary gonadotropic hormone* (gland extract) supplemented by *estrogenic substance*, which has a favorable influence upon the development and re-establishment of the secondary sex characteristics.

"The 2 cases reported responded favorably to anterior pituitary gonadotropic hormone in doses of 1 to 2 cc hypodermically 3 times weekly, and *emmenin*, 1 dram, once or twice daily. (In addition, *Case 1* received *A. P. L. hormone* (antuitrin-S), at the onset of treatment.) Both preparations were given in 3- to 4-week courses with rest period of 2 to 6 weeks, depending upon the response to therapy and the ability of the patients to

return regularly for treatment. At present, 2 other patients are being treated with A P E (anterior pituitary extract) and estrogenic substance with favorable response.

"Thyroid extract may be indicated as a metabolic stimulant in spite of weight loss. Plenty of rest and a high caloric diet are valuable adjuncts."

CASE 1—A white female, aged 18 years. The onset of the loss in weight and associated symptoms was at the age of 15. She had not menstruated by 16½ years of age, and the secondary sex characteristics had not appeared. At 16½ years of age the patient measured 57½ inches, and weighed 69¼ pounds. The external genitalia corresponded to that of a child of 10 years. The thyroid gland was small, the pulse 68, regular, and low tension. The heart was of the asthenic type. Blood pressure was 90/52. The B M R was minus 8, serum cholesterol 157 mg. Quantitative determination of urinary prolactin and estrin failed to reveal either hormone. The blood showed a secondary anemia with no eosinophilia.

The therapy was from 16½ to 16¾ years, 23 injections of *antuitrin-S*, with an increase in weight from 69¼ to 73 pounds. After 8 injections the patient experienced pelvic cramps. From 16¼ to 17 years, courses of *anterior pituitary gonadotropic hormone* (Maturity Factor, Ayerst) 1 cc subcutaneously 3 times weekly. During this period her breasts began to develop, and pubic and axillary hair became more abundant. At 17 years her weight was 77 pounds. Between 17 and 17½ years, several courses of Maturity Factor alternated with *emmenin* orally. At 17½ years she "spotted" for the first time. Her height was 60 inches, and her weight 81½ pounds. At 17 years 7 months, another course of pituitary gonadotropic hormone as she had not menstruated beyond the 1 period of spotting. One month later she experienced her first menstrual period. At this time her height was 61 inches, and her weight 86½ pounds. During the past 4 months, her menstrual periods have been normal. At 18 years, her height was 62 inches, and her weight 97 pounds. The secondary sex characteristics were normal. Over the 1½ years of therapy the growth gain was 4½ inches, and the weight gain 27¾ pounds.

CASE 2—A white female, aged 20 years. The onset of a rapid loss in weight and asso-

ciated symptoms was at 15½ years of age. Just prior to this, the patient had menstruated for the first time. Since then until 18 years of age there had been only 2 scant periods. All x-ray and laboratory studies were negative. At 18 years of age the patient measured 63 inches and weighed 81 pounds. The diagnosis from the gynecological examination was marked genital underdevelopment suggesting aplasia or extreme hypoplasia of the ovaries and breasts, extremely hypoplastic uterus and arrested secondary sex characteristics. The B. M. R. was minus 11.6. Heart, normal. Examination of the urine for prolactin and estrin failed to reveal either hormone.

The patient has received periodic treatment with anterior pituitary gonadotropic hormone and estrogenic substance. Her menstrual periods became established at 19 years, and are now regular.

Pituitary Dwarfism

Treatment—N. M. Taylor¹⁷ reports favorable therapeutic results in 7 of 8 cases of pituitary dwarfism (7 males, 1 female) between the ages of 11 and nearly 16 years, treated with 2 cc. or (in 1 case) 3 cc. of *anterior pituitary growth hormone—antuitrin-G*—3 times weekly, and *thyroid extract* in dosage suitable to individual tolerance, the treatment being continuous for 2 years or more in 3 cases, over 1 year in 4 cases, and for 8 months in 1 case.

When treatment was instituted the age of the boys ranged from 11 years 2 months to 15 years 9 months, and that of the 1 girl was 15 years. All cases received growth hormone therapy in the form of antuitrin-G, and all but 1 received thyroid extract concomitantly. Six cases received 2 cc. thrice weekly, and the girl, 3 cc. thrice weekly. The thyroid extract (Emplets-Parke-Davis Co.) ranged in individual tolerance from 5 to 11 grains daily. The seventh boy received 2 cc. of the antuitrin-G thrice weekly for 7 months, but the response was relatively unfavorable, so that dosage was increased to 5 cc. thrice weekly.

This failed to elicit any more marked growth, however. Although he showed the least response in the series, his growth at the end of 1 year exceeded the normal increment by 0.2 inch.

Of the cases eliciting favorable therapeutic response, 1 grew at the rate of 5 times the presumed increment, 1 trebled, and 3 more than doubled the growth anticipated on the basis of previous development. Also, 1 quadrupled and 4 more than doubled the normal increment for each individual age period. The annual increment ranged from 1.9 to 3.0 inches, and 1 had an increment of 22 inches in 6 months.

In none of the cases treated for more than 1 year was there shown any evidence of a refractory period, or a time at which response to therapy failed. In the 3 cases treated for 2 years or longer, growth in the second year actually exceeded that of the first year. There was evidenced no phenomena which might be interpreted as representing a production of antihormone.

Pituitary Basophilism

Surgical Treatment—A. R. D. Pattison and W. A. G. Swan¹⁸ state inhibition of the secretory activity of the anterior pituitary gland is justifiable in cases of Cushing's syndrome where the presence of an adrenal or thymic tumor has been excluded. Should deep radiotherapy fail to accomplish this, then the *implantation of radon seeds into the pituitary* should be performed.

This operation, performed on the 2 cases reported, was as follows: The region of the sellar diaphragm was exposed and 2 small longitudinal incisions were made in the diaphragm through each of which 2 radon seeds were inserted into the sella. The radon seeds were of 2 millicuries dosage each with gold screen-age

The first case, a woman aged 26, exhibited abdominal obesity, hirsutism, cutaneous striation, amenorrhea, vascular hypertension, hyperglycemia, polycythemia, and slight skeletal decalcification, but gave no evidence of an adrenal or thymic tumor. She experienced only slight improvement following 3 courses of radiotherapy. The insertion of the radon seeds produced a much greater and more sustained effect, as evidenced by a lowering of the blood pressure and hemoglobin percentage, and a return of menstruation.

The second case, a girl aged 16, exhibited the same symptomatology, but with greater skeletal decalcification. Radiotherapy and the removal of part of the anterior appeared to have no influence on the disease, but there was much improvement following the insertion into the pituitary of 3 radon seeds, each of 3 millicuries with platinum screenage. There was histological verification of the diagnosis of this case, as the anterior pituitary showed the typical Crooke cells.

The authors do not feel the implantation has provided a "cure" for the disease. Nevertheless, following the operation there was considerable improvement and complete removal of the menace of a progressive hypertension in both cases. The results from the 9 millicuries in the second case were not strikingly different from those exhibited with the 4 millicuries in the first case, but this may be due to the fact the seeds in the first case were more favorably placed for influencing the pituitary's activity, owing to the shape of the sella turcica.

Both patients are in excellent subjective health, but there has been little change in their external configuration. However, their general appearance has been greatly improved by the disappearance of the facial hirsuties and plethora.

ANTERIOR PITUITARY-LIKE PRINCIPLE

Influence on External Genitalia of Young Boys

W. O. Thompson, N. J. Heckel and A. D. Bevan¹⁹ report 28 patients between the ages of 1½ and 37 years with undescended testes, treated with an anterior pituitary-like principle (*follutein*, "A. P. L."), in whom the rate of successful results therefrom was 22 per cent or, if 7 patients of over 15 years be excluded, 33 per cent.

In this group, no descent was produced in any patient over 12 years of age. The condition was bilateral in 11, 3 of whom had had a unilateral orchidopexy prior to institution of therapy. Thus there were treated 36 undescended testes in the 28 cases. In 22 instances the testes were in the inguinal canal, in 14 they were within the abdominal cavity. Descent occurred in 8 instances, 1 case showing bilateral descent. In the successful instances, where the data was extensive enough to warrant conclusions, the descent occurred within 9 weeks. In the 8 patients who underwent operative measures when the prolonged A. P. L. treatment failed to produce descent, anatomical factors were found to have blocked the therapeutic effect. The therapy was therefore successful in 25 per cent of the patients, or in 22 per cent of the total number of undescended testes; and if, as has been noted, the 7 cases over 15 years of age be excluded, the percentages rise to 33 and 32, respectively.

The commercial A. P. L. principle used was follutem (Squibb) and "A. P. L." (Ayerst). Although the strength of each is expressed in rat units, the methods of standardization are different; the R. U. of follutem is stronger than that of "A. P. L.," but no quantitative comparisons between the 2 are yet available. The

close varied from 100 units 3 times weekly to 1000 units 6 times weekly in all but 2 patients, 37 and 30 years respectively, who received 3000 units daily.

In discussing the 8 instances of descent which this material produced in 7 patients, the authors point out that 5 were of the type that commonly descends at puberty, *i. e.*, they could be pulled down to a level between the extreme lower end of the canal and the upper end of the scrotum before treatment was started. Thus there were only 3 testes in the canal to prove absolutely the profound influence of the material. However, the prompt descent in the successful cases is to be noted, particularly that of Case 1, in whom the descent of the left testis, despite its being high in the canal, occurred at the end of a total 625 units of follutein or early in an additional 3-week course of 550 units. Another case had descent of the right testis from the middle of the canal after a total dosage of 2125 units of follutein.

The most striking influence of this material was evidenced not so much in the descent of the testis as in the growth of the genitalia. Genital growth was produced in 15 of the 28 patients, and in 11 it was marked. These changes occurred in most instances so much before the age of puberty that there can be no doubt of their being the result of therapy. A condition simulating premature puberty was produced in 2 patients 7 and 9 years old with undescended testes and in a boy 4 years old with one atrophic testis. The penis became as large as that of an adult. There was also enlargement of the scrotum and the prostate, a growth of pubic hair, a change in the pitch of the voice and, in one instance, a growth of hair on the side of the face. The increase in size of the prostate seemed coincidental with that of the penis. The boys showing an increase in the size of the genitalia be-

came more virile and belligerent. This increase in size of the genitalia appeared more markedly before the age of puberty, but it did occur in a man 37 years old. It is to be advised, however, that excessive genital growth can be avoided by careful control of the duration of therapy and close observation of the patient.

The material may be of further therapeutic value in (a) facilitating operative correction of hypospadias and epispadias: by enlarging the penis and scrotum, the treatment being given for at least 2 months to all patients with undescended testes, regardless of the age; (b) following operation for undescended testis when the testis has not been brought to a sufficiently low level: Cited, descent in 2 of 5 cases; and (c) in the treatment of hypogonadism. Cited, growth in 9 of 12 patients, largely of the Frohlich type.

Precocious Sexual Development from an Anterior Pituitary-like Principle

W. O. Thompson and N. J. Heckel²⁰ report 3 cases of young boys with undescended testis, 2 of whom received treatment with follutein and 1 with A.P.L. and maturity factors, which resulted in the development of a syndrome simulating premature puberty.

The first case was a boy, aged 6 years and 7 months, with failure of descent of the right testis. His body contour was normal, but he was slightly short for his age. In the erect posture the right testis was at the level of the external ring, but could not be displaced downward. There was question of a right inguinal hernia, accounting perhaps for a painful swelling which had occasionally occurred since the age of 2 months. The penis measured 3.8 by 1.9 cm. and the left testis 2.2 by 1.2 cm. The prostate was not palpable. Treatment with *follutein* was instituted, the dosage being rapidly increased until

200 R U were being given 6 times a week.

The growth changes in response to the follutein were immediate and rapid. At the end of 1 month the right testis was felt just above the upper end of the scrotum with the patient in the upright position and could be pulled into the upper end of the scrotum. The penis and scrotum were larger, the prostate was about 2 cm in diameter, and erections were more frequent. There were several pubic hairs as much as 0.9 cm long, and the voice had begun to lower in pitch.

As the therapy was pursued the increase in size of the penis, scrotum and prostate, and the development of pubic hair continued to be rapid. At the end of 2 months, after a total of 7570 units, the penis had grown 1.3 cm. The further increase in size of the penis was about as great at the end of 4 months, 7 by 3 cm, as at the end of 11 months, 7 by 3.2 cm. At the end of 9 months, after a total dosage of 47,370 units, the right testis was small (0.7 cm in diameter), hard and still in the upper end of the scrotum, lying attached to a pouch that had first been noticed after 1 month's therapy, and which by this time had enlarged and extended more than 2.5 cm downward from the upper end of the scrotum.

The penis now measured 7.3 by 3.2 cm (larger than his father's), and the left testis measured 2.5 by 1.4 cm. The left testis was at a much lower level and the scrotum was much larger than before treatment was started. The prostate was the same as after 8 months' therapy, about 3 cm in diameter. The pubic hairs were abundant and measured as much as 7 cm long. Erections continued to be frequent.

One year after institution of therapy, operative measures had to be undertaken for a strangulated hernia. The operation disclosed at the upper end of the scrotum

an atrophic white testis about 1.5 by 0.7 cm in size. A tunica vaginalis was formed from part of the peritoneal pouch and the testis placed in the scrotum.

The B M R. taken at the beginning of treatment showed minus 11. This fell to minus 16, 7 months later, but subsequently returned to minus 10. The increase in weight and height during the first 7 months, the period which also showed the greatest genital development, was 4.2 kg and 9.5 cm. At this same time the epiphyseal lines of the knees and elbows showed about normal development, and 4 months later there was no evidence of any premature closing.

The second case was a boy, aged 9 years and 1 month, with undescended testes. Operative procedures had failed to bring them to a sufficiently low level. Each testis was about the size of a "small cherry," and was located at the junction of the scrotum and the opening above. Associated with each testis was a small hernia. The penis measured 4.1 by 2.2 cm. The prostate was barely palpable. The pubic hair was just a fine fuzz.

Treatment with follutein was instituted, the dosage being rapidly increased to 200 R U 6 times a week. Within 11 days, after a total dosage of only 1520 units, the penis had increased 1.3 cm, and the prostate was about 2.5 cm in diameter. Erections had become more frequent. There was no definite change in the position of the testes. At the end of 2 months, after a total dosage of 7720 units, each testis was the size of "a large cherry," and seemed to be at a slightly lower level. At the end of a little over 4 months, after a total of 17,320 units, the penis measured 7 by 3 cm, which was about as large as it was at the end of a year's therapy. The prostate was about 2.5 cm in diameter. The testes were at a slightly lower level in the scrotum, which was enlarging. The pubic hairs

had grown slightly. Soon the boy's voice was lower in pitch, he was aggressive, and his muscles were hard. The testes continued to descend a little. At the end of 8 months' therapy the penis measured 7.6 by 3 cm., the right testis 3.2 by 2.4 cm and the left testis 3.5 by 1.9 cm. But at the end of a year's therapy, after a total dosage of 34,720 units, the penis measured 7 by 2.9 cm, the right testis 2.5 by 1.9 cm. and the left testis 3.2 by 1.9 cm. The pubic hairs were the same as 2 months previously, scanty but as long as 5.1 cm.

Before commencing therapy the B. M. R. had shown a minus 4. At the end of 9 months it showed a minus 5. During this same period the weight gain was 8.5 kg. and the height gain 9 cm. X-rays of the knees and elbows, first done 8 months after institution of therapy and again 8 months subsequent to that, showed the development of the epiphyses to be normal.

The third case was a boy, aged 4 years and 11 months, with a supposed failure of descent of the left testis. It was first thought the peritoneal process was felt in the scrotum on the left, but the testis itself was not felt. However, the subsequent finding of a small atrophic mass on the left side of the scrotum suggests the testis to have been in the scrotum but was not felt due to its small size. It is also possible that the treatment may have produced descent of this small atrophic testis. The penis measured 3.8 by 1.6 cm and the right testis 2.9 by 1.7 cm. Treatment with A. P. L. and maturity factors was instituted, the dosage being rapidly increased to 200 R. U. of A. P. L. and 25 R. U. of maturity factors 6 times a week. Within 8 days, after a total of only 1120 units of A. P. L. and 150 units of maturity factors, the penis measured 4.1 by 2.9 cm and the right testis 3.8 by 2.9 cm; the left

testis was reported not palpable. The prostate was not palpable.

Five weeks later, after a total of 4320 units of A. P. L. and 550 units of maturity factors, the penis measured 6.7 by 2.1 cm. and the right testis 3.2 by 1.7 cm. A small mass on the left side of the scrotum may or may not have been the left testis. The prostate had enlarged, and erections had become more frequent.

One month following this the dosage was increased. A. P. L., special strength—500 R. U. per cc instead of 100 R. U. per cc—was employed. Thus the dose was 1000 R. U. 6 times a week. The dose of maturity factors remained unchanged.

After 4 months of therapy, with a total dosage of A. P. L. 29,020 units and maturity factors 1925 units, the penis measured 7.3 by 2.4 cm. and the right testis 3.8 by 2.1 cm. The scrotum was unusually well developed for his age. A small nodule about 0.4 cm had appeared on the left side of the scrotum and was thought to be the left testis. The prostate was full and measured about 3 cm. in diameter. There was a definite growth of pubic hair, which was as much as 2.5 cm long. Although some of the injections were missed, after 7 months' therapy, with a total dosage of A. P. L. 55,020 and maturity factors 3225 units, the penis measured 6.7 by 2.5 cm and the right testis 3.2 by 1.6 cm. The small nodule on the left was thought to be the left testis, since what seemed to be a vas deferens was felt above it. The left side of the scrotum was not so well developed as the right. The prostate bulged into the rectum and was about 2.5 cm. in diameter. Pubic hair was as much as 3.8 cm long. It was not known whether the little hair on the side of the face was due to the

treatment or not. Any huskiness in the voice was debatable.

Four B. M. R. readings over the 8-month period showed from plus 1 to minus 10. The weight gain had been 2.1 kg and the height gain 2 cm. X-rays done 3 months after institution of therapy showed the ossification center for the capitellum was present in the elbows. No other ossification centers were seen. All the ossification centers were present and well developed in the knees.

In summary, there was a marked increase in the size of the penis, scrotum and prostate and the development of pubic hair, which was in striking contrast to the lack of definite increase in size of the testis. The testes remained small in comparison with other parts of the genitalia. The growth of the genitalia seemed to reach a maximum quickly. The special strength A. P. L. did not seem to produce any greater influence on the size of the genitalia than the smaller dose. A marked susceptibility to the growth stimulus of A. P. L. has been noted in other cases, small doses obtaining remarkable increase in size of the genitalia. The susceptibility to this stimulus appears to be greater before puberty, although it is not entirely absent after puberty. This material has produced genital growth in a child 3 years old and in a man 37 years old. The mechanism of the growth response is not precisely defined. It is not known whether spermatogenesis occurred in the 3 cases reported.

Antihormone Studies in Boys Treated with Anterior Pituitary-Like Hormone for Genital Underdevelopment

G. B. Dorff,²¹ reports his studies in 19 boys between the ages of 7 and 13 years, having genital underdevelopment varying from genital hypoplasia to intra-

abdominal cryptorchidism, treated, and being treated, with some commercial brand of A. P. L. principle from the urine of pregnant women, whose sera at no time revealed the presence of anti-hormone, either during treatment or (2 cases) 21 to 24 months after discontinuance of therapy.

The total amount of A. P. L. hormone administered to any one patient varied from 11,200 R. U. given over a period of 3 months, to 112,300 R. U. given over a period of 17 months. The commercial brands used were, follutein, antutrin-S, antophysin, and "A. P. L."

With the exception of 2 cases, all specimens of sera were taken for examination during the course of treatment with A. P. L. hormone, at a time when it was thought the patient had received sufficient hormone to develop any antagonistic substances. In the other 2 cases, sera were sent for examination, not during, but after treatment with A. P. L. hormone had been discontinued for 21 and 24 months respectively. In all, 20 tests were made on the 19 cases, 1 patient undergoing 2 tests at different periods.

In discussing the cases, the author admits there were times, in cases with marked underdevelopment who were receiving intensive therapy, that the possible existence of antagonistic bodies was suspected. This was at the period of an apparent occasional relative slowing-up of progress, or when there was a suggestion of a halt in the development. The dosages were then increased, or the product changed, and with these changes the sluggish responses or retardation in progress were overcome, so that progress was resumed, and eventually in most cases the hoped-for results were attained. If no antihormone exists, the slowing-up or halt in the progress might be, and more than likely is, caused by a

tolerance in the patient to the particular brand of A. P. L. hormone used so intensively.

There were, however, cases of a severe type, especially those presenting intra-abdominal cryptorchidism and the occasional case of inguinal cryptorchidism, where even increased doses and intensive treatment, or a change of product, failed in any testicular formation or in complete descent of the testes after descent had begun. The author again admits the possibility of antihormone formation being a likely cause for the unfavorable period, but points out that, although testicular descent could not be accomplished, there was always enlargement and development of the existing hypoplastic gonad, and stimulation and development of the secondary sex characteristics. This was evidenced by marked sexual skin congestion, enlargement and even hypertrophy of the penis, development of the scrotum, and production of suprapubic hair. The author feels such evidences of stimulation and development of the secondary sex characteristics precluded the existence of antihormone even though, in several cases, the cryptorchidism could not be corrected. He nevertheless admits it would be imprudent to negate the antihormone theory since only 20 blood tests were made, despite the fact they were all negative. In the author's view, a true mechanical obstruction existed in those few cases where neither increase in dosage nor change in product could initiate or complete the descent of the testes.

Clinical Indications for Anterior Pituitary-Like Sex Hormone

R. L. Schaefer, E. A. Sharp and J. V. Lammy,²² present a comprehensive report on the clinical application of the A. P. L. principle (antuitrin-S), exemplified in 16 cases of genital hypoplasia

and cryptorchidism, 15 cases of amenorrhea, and 13 cases of menometrorrhagia, in which the therapeutic results were uniformly good where treatment was indicated.

They feel that the A. P. L. extract from the urine of pregnancy, usually regarded as containing follicle-ripening and luteinizing factors, has a presumptive indication for clinical use by reason of its gonad-maturing action demonstrated in immature female rats. In theory, therefore, its obvious application should be in subjects manifesting delayed sexual development. The basis of the authors' report is the practical demonstration of this theoretical sex-maturing action.

The potency of the A. P. L. extract from the urine of pregnancy used in these cases, antuitrin-S, is expressed in rat units determined by the induction of corpora lutea within 96 to 100 hours when the extract is injected in 6 doses (twice daily for 3 days) into female white rats 26 days of age. One rat unit is the minimum quantity of urine extract which will cause the formation of 1 or more corpora lutea under the aforementioned conditions. Since the age of the rats, food and other factors modify bioassays of a quantitative nature, rats in this test are selected from a colony the members of which are known to become sexually mature in 50 to 60 days. The accuracy of the assay is further enhanced by using a group of 10 or more animals on each dosage and accepting as the minimal effective dose that which induces corpora lutea in 60 per cent of the group.

Of the 16 cases exhibiting genital hypoplasia and cryptorchidism, 13 had Frohlich's syndrome, 4 of which also manifested cryptorchidism, 2 were cryptorchids of normal statural endocrine type and 1 was a case of infantilism

The results were uniformly good in all but 2 cases: 1 in whom surgical procedures were very likely necessary, the other, the case of infantilism, who was probably incapable of response to adequate normal pituitary stimulation (male gonadal hormone rather being indicated). The ages ranged from 7 to 19; the duration of therapy, from 1½ months to 1½ years with periods of no therapy inclusive; the dosage, from 2 cc. twice weekly to 5 cc. thrice weekly, the average being 3 cc. thrice weekly; the total dosage, from 3600 R. U. to 31,200 R. U. The cases showing obesity and a decreased B M R were given, in addition, a low caloric diet and thyroid extract to tolerance.

The authors stress that although there is a theoretical objection to the administration of any substance capable of producing sex precocity (as there may be in turn early epiphyseal closure), there is no contraindication at any age level, if the material is used wisely for 3- to 6-week periods in the dosage indicated. They further point out the utter fallacy of withholding hormonal treatment from such patients in the hope nature will strike a balance.

The amenorrheic group, ranging in age from 13 to 28, included 4 presenting also a typical adiposogenital pituitarism. All cases were regarded as having gonadal immaturity. Hence *theelin* was used in conjunction with the **A. P. L. factor**. The A P L extract was given whenever possible for 2 weeks immediately following a period of bleeding, with the *theelin* being given during the 2 weeks preceding the expected menstrual period as a replacement agent. This series of injections was repeated, then followed by an initial 2-week and a subsequent 3-week rest period, "in the expectation that the alteration of treatment would eventually coincide with

the proper hormonal phase of the menstrual cycle." All patients showed a response to treatment, if the establishment of the menstrual cycle may be considered as such. The authors admit there has not been time enough to permit proof of maturation of the ovary. The average dosage was, antutrin-S, 2 cc. 2 to 3 times weekly for 2 weeks, then *theelin*, 1 cc. 2 to 3 times weekly for 2 weeks. The duration of therapy ranged from 3 months to 3 years.

The patients with menometrorrhagia ranged in age from 20 to 47 years. The response to the A P L extract in 6 cases was entirely specific. The authors feel that the beneficent effect of the gonadotropic extract was due to the bleeding being associated with immature state of the gonads. The other 4 cases, whose age range was 40 to 47 years, were treated with larger doses of the A P L factor to show, in contrast to younger women's almost specific response to this therapy, the indifferent or variable effect on bleeding when the gonads are in the menopausal or senescent stage of function. The dosage in the 6 cases ranged from 2 to 4 cc. of antutrin-S twice to 3 times weekly. In the 4 cases the dosage ranged from 2 cc. of antutrin-S twice weekly to 2 to 10 cc. daily, the maximum for 2 weeks only.

The authors advise that treatment be prolonged and continuous before concluding that the existing imbalance cannot be corrected. Further, in their opinion, the anterior pituitary-like sex hormone is the maturing factor of the gonads.

THE SEX HORMONE EXCRETION FOR CHILDREN

R. B. Oesting and B. Webster,²³ report their determinations of the androgenic and estrogenic excretion of children, based on the 24-hour urine

specimens from 43 boys and 16 girls between the ages of 3 and 15 years, which reveal the androgenic excretion to have a gradual rise from early childhood to adult life, and the estrogenic excretion to have, contrariwise, a distinct rise at puberty

At 3 years of age, in the boys, the male hormone excretion was either a trace, 27 or 56 I. U. per 24 hours. The high for 6½ years of age was 11.2 I. U. per 24 hours. The high at 9 years of age was 16 I. U. per 24 hours. The appearance of female hormone in the urine did not occur in assayable quantity until 12½ years of age, when 10 I. U. of estrone were determined. The highest determination was 30 I. U. of male hormone and 30 I. U. of estrone in a child of 13. The determination at 15 years of age was 24 I. U. of male hormone and 50 I. U. of estrone.

At 3½ years of age, in the girls, the excretion of male hormone was 2 I. U. per 24 hours. This increased until, at 10 years of age, 11.2 I. U. per 24 hours were determined. At this time the first assayable quantity of female hormone appeared, 10 I. U. of estrone. The highest determination was at 13½ years of age, when there was found 20 I. U. of male hormone and 80 I. U. of estrone per 24 hours. The highest determination of female hormone at 14 years of age was 80 I. U. of estrone, with 18.7 I. U. of male hormone per 24 hours. Another child at this age had 22.7 I. U. of male hormone and 30 I. U. of estrone per 24 hours.

It may be seen, therefore, that there was a gradual rise in male hormone excretion from early childhood on through puberty, since the average adult excretes 40 to 50 I. U. of androgen per 24 hours. The much smaller amounts of estrogen produced and the distinct rise at puberty lead to the hypothesis that

puberty, as affected by androgens, is a somatic threshold reaction, and that the increase in estrogens at puberty and their action combined with male hormone plays a more important part in the development of the adult form and in the closing of the epiphyses and other changes of puberty. This is emphasized by the observation, boys do not excrete estrogens in measurable amounts until they reach the age of 13 or more, whereas girls of 10 to 12 are already excreting estrogens. Although unconfirmed, this may indicate the earlier arrival of puberty in girls.

THE TESTES

Observations on the Male Climacteric

H. R. Donald²⁴ presents an excellent and comprehensive survey of the male climacteric, which he defines as "not a definite epoch, but an ill-defined state of potential nervous instability, characterized by certain modifications in physical structure and by a great variety of functional disturbances. The onset, intensity and duration of these nervous phenomena may be influenced by several conditions, but fundamentally they are the result of 2 principal intrinsic factors, namely, the basic neuroendocrine constitution of the individual, and the degree of glandular involution which occurs with age. The age of onset of the climacteric in males, as well as in females, is for this reason extremely variable." The age range of most of the author's patients was 50 to 70 years, but there were typical cases at 42 and 76 years. He offers 9 cases illustrative of the symptomatology and the results of therapy. He further stresses the insidious development of the climacteric state, and the rapid establishment of permanent

degenerative changes in the tissues, advocating, therefore, attentive early diagnosis and prophylaxis.

The results of urinary determinations for gonadotropic hormone have been confusing and contradictory, due to lack of standard methods of extraction and estimation. That there is a great reduction in the male hormone excretion after the age of 50 is agreed upon by most investigators, and no cyclical variation in excretion has been demonstrated in the male.

The clinical characteristics of the male climacteric reveal the functional disturbance is not confined to the gonads. Thus, mild and medium degrees of myxedema are relatively common, and true hyperthyroidism may occur occasionally. There have been cases of diabetes and, in the author's experience, several cases with symptoms strongly suggestive of cortical deficiency and even of Simmonds' cachexia. Therefore, the occurrence of such polyglandular disturbances must be carefully borne in mind.

Of the physical changes, the somewhat average tendency to put on weight is less significant than the almost constant changes in the distribution of subcutaneous fat. This commences to collect both within and on the walls of the abdomen, with pads of fat appearing above the pubis. This change in configuration occurs even when the body weight may be declining, thus making the body more pear-shaped. The hair growth becomes less vigorous, and there is a gradual regression to neuter type.

But most typical of all are the psychological changes, which are a progressive loss of physical and mental energy, lessening of concentrative powers and self-confidence, and decline of satisfaction in former interests and pleasures, with a characteristic unreasonable depression and pessimism. There may

sometimes be an increased sexual desire, more than likely from psychological reasons, but more often there is a waning sexual interest.

Most of the changes in function are due to instability of the autonomic nervous system, with only a few being of endocrine origin. The circulatory changes, such as diffuse or localized peripheral arterial spasm affecting the limbs, the head, and the coronary or retinal vessels, are of utmost importance as they may ultimately be responsible for ischemic degeneration. A usual cardiac complaint is palpitation. The functional "heart attacks," which are not uncommon, end very often in characteristic drenching perspiration. The changes in respiratory function are important because of the fibrotic changes which may quickly become established in the lungs, and are usually characterized by catarrh in the upper passages, tightness of the chest, and spasmodic asthma. The gastrointestinal tract is often mildly attacked, but there are also frequent biliary or renal calculi giving rise to trouble. A very common complaint is frequency of nocturnal urination; there may also be enlargement of the prostate. The skin may be affected by the circulatory changes. (The author has had several cases of angioneurotic edema, particularly of the face, who responded very well to treatment.) And the eyes are very often deeply affected.

When diagnosing, great care must be taken to exclude organic conditions, such as tumors, infections of the upper respiratory tract, and renal and cardiac insufficiencies, and yet, after this has been done the true origin of the symptoms often remains doubtful. When this is the case, the author recommends that testosterone propionate therapy be given a trial. It is pointed out, however, that improvement on this treatment will be

in relation to the extent of gonadal responsibility. On this factor, and the extent of established organic change, is the prognosis dependant.

Treatment—The author begins his treatment with injections of 10 mg. of *testosterone propionate* on alternate days, reducing the dose as soon as the symptoms are controlled. Subsequently the regular intramuscular administration of 5 to 10 mg. twice to 3 times weekly is sufficient for the average case. Improvement has usually occurred within a week or 10 days. The duration of treatment is extremely variable. The dosage in some cases may be radically reduced in 6 months, but in others it may have to be maintained for 12 months or longer.

The improvement from the treatment is in some cases almost dramatic. The psychological symptoms are generally relieved before the functional disturbances. The patient feels stronger, his energy and outlook are much better; the whole tone of his physical and mental setup becomes greatly improved. If there is no gross organic change, the same improvement will be noted in visceral function. The breathing becomes easier, the tightness in the chest disappears, and the nocturnal asthma often obtains amazing relief. Angina pectoris and cardiac attacks may be absolutely controlled. The frequency of nocturnal urination and the abdominal disturbances often respond with great rapidity.

Several of the cases are as follows. Case 2, aged 58, with a nocturnal cough for 6 months, and in addition, attacks of asthma and pronounced physical exhaustion. The attacks of asthma were occurring regularly every night at the time of examination. His weight had been increasing for the last year. His libido had been absent for 3 or 4 years. Any exertion was followed by prolonged

dyspnea. After 2 weeks' treatment of 5 mg. of testosterone propionate twice weekly he felt much better in every way, but the asthma was still present. Six weeks after beginning therapy he was free of asthma, and felt greatly improved in every way.

Case 7, aged 53, with severe pain, usually localized in the epigastrium but sometimes in the left iliac fossa, for 12 months. There was a constant feeling of nausea, and vomiting occurred 2 or 3 times weekly. After 2 months' treatment of injections twice weekly of 5 mg. he was completely free of symptoms.

Eunuchoidism

Effect of Testosterone Propionate on the Genitalia, Prostate, Secondary Sex Characters, and Body Weight—A. T. Kenyon²⁵ reports 4 eunuchoids treated with 25 mg. daily of testosterone propionate, subcutaneously, from 5 to 7 times weekly for 28 to 99 days, of whom 3 received extended treatment of 10 to 25 mg. 3 to 7 times weekly, with interruptions, until the 146th, 108th, and 163rd days. The results were an early increase in erections in all 4 cases, enlargement of the penis in 3, enlargement of the prostate in 4, distinct deepening of the voice in 2, an increase in sexual hair in 1, hypertrophy of breast tissue in 1, no change in the size of the testes in 2 cases studied (but sperm disappeared during treatment in 1 of these, to reappear later). There was a marked increase in body weight in all 4, accompanied by increased appetite in 2 and by evident edema in 2. There was a slight increase in the B. M. R. of 1.

The eunuchoidism reported had the symptoms of testicular deficiency. The testes were retained in the abdomen or, if in the scrotum, were small. The penis and prostate were hypoplastic. Erections

usually occurred, but ejaculation was absent or scant, with few or no sperm. The excretion of androgens in the urine, in these and in other studies, averaged about a third of that in the normal, but the values for low normal may be overlapped. Estrogens have likewise been diminished. Treatment of this condition in the adult with pregnancy urine has as a rule been unsatisfactory.

The decision of the dose of testosterone to be used in the treatment of eunuchoidism may be based on the fact the average normal excretion of androgens in the urine of young men amounts to about 70 I. U. daily. This represents the activity of 7 mg. of androsterone, or 21 mg. of dehydroisoandrosterone, both of which substances are present in normal urine. It is very probable that a calculated daily loss through the urine of 7 to 21 mg. of testosterone represents only a fraction of the total testosterone disposed of by the organism. The daily dose of 25 mg. testosterone propionate selected for this and other studies is not, therefore, unreasonably high.

A more complete summary of the results in the 4 cases reported is as follows. Cases 1, 2 and 4 received 97.5, 177.5 and 55 mg. of testosterone, in 2.5 mg. doses, in 76, 123, and 24 days, respectively. In Cases 1 and 2 there was an increase in erections and an elongation of 1 cm. or more in the penis, and in Case 1 the development of small buttons of breast tissue, but in no instance did prostatic tissue increase clearly in amount. In Case 2, 125 mg. of testosterone propionate in 5 mg. doses in 34 days was given with the production of increased erections and further elongation of the penis by 1 cm., but again no change appeared in the prostate. The absence of prostatic change, together with the theoretical considerations of the proper dosage, led to continuing with

larger amounts of testosterone propionate.

Thus Cases 1, 2, 3 and 4 received 25 mg. of testosterone propionate, subcutaneously, from 5 to 7 times weekly for 28 to 99 days. Thereafter, Cases 1, 2 and 3 received 10 to 25 mg. 3 to 7 times weekly, with interruptions, until the 146th, 108 and 163rd days respectively. In all there was an early increase in the frequency of erections and a marked increase in the size of the prostate (day 12 to 36) with recession after discontinuance in the cases studied (2 and 4). The penis elongated from 1 to 2 cm. in all but Case 3, but this enlargement did not progressively increase during the course of treatment. Enlargement of the scrotum was not especially striking. In Cases 1, 2 and 4 there was a distinct deepening of the voice (day 27 to 95, 26 to 36, 28), and the exception, Case 4, had a fairly deep voice to begin with. In Cases 1 and 2 there was a striking development of hair in the pubic area, up the linea alba, over the thighs and on the face (days 95, and 64 on), whereas in Case 3, who was further advanced to begin with, the hair increase although distinct was more moderate (day 54 on), and Case 4, who was treated for 28 days, showed no change in hair growth. Recession in the size of the penis and of the prostate after stopping treatment occurred in the 2 cases already mentioned (2 and 4), in which opportunities for such observations were provided. In Case 1, nubbins of breast tissue, 3 by 2.5 cm. in diameter, appeared under the nipples, and in this and Case 2 a slightly opalescent fluid could be expressed therefrom. In the 2 cryptorchid patients (1 and 2) the testes did not descend, but in view of the scars of previous surgery the integrity of the tissue in and about the inguinal canals had been destroyed. The 2 with testes in the

scrotum showed no changes whatever in either the size or consistency of these organs, although careful measurements were made. In Case 3, the few sperm, which had been present in the semen consistently for 5 months, disappeared during treatment and reappeared 1 month after discontinuance. An acneiform eruption appeared on the face of this 1 patient. Libido was increased in Cases 1, 2 and 3.

Remarkable and, at the time, completely unexpected was the consistent and considerable gain in body weight. In the 4 cases the gain in 10 days was 1.5 kg. in Cases 1, 2 and 3 and 2.0 in Case 4. The maximum gain of 4.5 to 8.5 kg. was reached in 28 to 65 days. Only in Cases 1 and 3 was treatment continued after this high point, and in both a plateau was established. Fullness and puffiness of the face was present in all, puffiness of the hands in Case 1, and definite pitting edema of the legs in Case 4. In 2 (Cases 1 and 2), the appetite was greatly stimulated. Reduction of the dose of testosterone propionate led to a loss in weight in Case 1, discontinuance to a loss in 2 (Cases 3 and 4) but in Case 2, in which the edema was not obvious, a loss of 1 kg. only occurred in 29 days after stopping treatment. The B M R determinations on Case 3, showing if anything a slight rise, indicate that lowering of the basal caloric requirements plays no part in the weight gain.

The author comments that the neuro-circulatory mechanism for the erection of the penis seems, in the hypogonad, to be most sensitive to increases in the male hormone content of the body. This augmented irritability often appears within 24 hours of the initial injection of 25 mg. of testosterone propionate. The effects in children and the regularity of the observations in adults would

seem to suggest very strongly that the androgens do really increase frequency of erection in certain conditions in man.

While the physiological significance of this remains as yet obscure, the author offers 4 possibilities suggested by the data presented, stating that only very carefully controlled work will disentangle them. (a) The erectile power of the penis in man is developed and maintained by the activity of the nervous system, and the male hormone acts in a supplementary fashion to excite this mechanism further, or to vary the threshold to psychic stimulation. (b) The nervous mechanism is entirely dependent upon the male hormone for its development and maintenance. This view requires the assumption that the very small amounts of male hormone circulating in the infant suffice, and that androgens of nongonadal origin so operate in castrates, maintaining their potency. (c) The mechanism is entirely nervous, and the apparent influence of hormones in these experiments is of no physiological significance, but rather to be interpreted as due to reflex stimulation from the penis, which is enlarging at an abnormal rate, together with the psychic receptivity of the patients. (d) The nervous mechanism is matured by hormonal influence, and may thereafter operate undisturbed in the absence of hormones.

The enlargement of the penis which, in these and other studies, occurred as a rule early in treatment, was not progressive to the point of forming a hypernormal organ. The slowness of the change on the whole was probably due to the fact the organ was not in any instance extremely hypoplastic to begin with. This change, together with the enlargement of the prostate, deepening of the voice and increased growth of body hair are of course to be expected

once the proper dosage is found, in view of the well-known effects of testosterone and its esters in animals. The minimal dose level required to produce these changes is as yet uncertain, but it is of interest that Case 2, whose prostate enlarged readily on 25 mg. of testosterone propionate daily, showed no change in this respect on 10 mg., 3 times weekly, or on 5 mg., 6 times weekly. It should also be recalled in considering dosage that from 7 to 21 mg. of testosterone must be metabolized daily in the normal man to account for the androgens in the urine, and that this amount probably constitutes only a fraction of that destroyed in the body. It is probable, therefore, that to secure conclusive results in the eunuchoid in a reasonable period of time one will not be able to go much below the dosage used in these studies.

The influence of testosterone propionate on the testes themselves is still an open question. Careful measurements showed no change in the size of these organs in Cases 3 and 4, despite practically daily treatment for 54 and 28 days respectively. In Case 3, however, a few sperm, consistently present before, disappeared during treatment to reappear after discontinuance. The influence on the seminiferous epithelium in man must be studied much further, but the results in Case 3 suggest that inhibition of sperm formation in already hypoplastic testes may be produced by testosterone propionate.

The stimulation of breast tissue in Case 1 by testosterone, on one occasion, and by testosterone propionate on another, is of interest. Hamilton has reported a similar finding in his eunuchoid, and several important observations of breast hypertrophy in animals after androgens have been reported. The common breast hypertrophy of the male

adolescent may thus be due to testosterone as such, although interconversion of the male hormone into some direct breast-stimulating substance is possible, in the light of the recent report of Steinach and Kun indicating an increased excretion of estrogens after the administration of testosterone to man.

The consistent gain in weight, accompanied by fullness of the face and occasionally by demonstrable edema, and occasionally by a marked increase in appetite is of the greatest interest. The precordial discomfort in Case 2, apparently produced by testosterone propionate, is the only deleterious action thus far known in these and other studies. Its mechanism is obscure, but it should nevertheless be borne in mind.

Testosterone Propionate

A. A. Loeser²⁶ reports the case of a girl, aged 14, with the essential features of hyperthyroidism, and the therapy pursued. 850 mg. of *testosterone propionate* administered over a period of 2 months, which obtained the considerable lessening of the thyrotoxic symptoms. The patient had an increase in weight, a decrease of the tremor to almost imperceptibility, and lessening of the exophthalmus.

In the same issue of the *Lancet*, p. 1121, reference is made to the report of 3 cases treated similarly by Dr. Levy Simpson. These cases exhibited marked improvement within 3 weeks. He feels that "started early, or continued for a long period, testosterone propionate might prove to have a fundamental influence on the course of exophthalmic goiter."

Effect of Testosterone Propionate on Testicular Function in Monkeys—

In view of the increasing use of androgenic hormones in the treatment of hypogonadism, and their suggested ap-

plication in cases of masculine sterility, the question of their ability to promote spermatogenesis becomes of prime importance.

S Zuckerman²⁷ finds testosterone propionate does not appear to promote spermatogenesis in monkeys. The experimental animals were 8 immature rhesus macaques, 1 drill, and 2 Hanuman langurs, in connection with which there was adequate control material.

The rhesus monkeys were given up to 400 mg of testosterone propionate over a period of 2 weeks, the drill received 5 Gm. over a period of 191 days, and the 2 langurs received 2 Gm and 1 Gm. for periods of 157 and 142 days respectively. No stimulation of spermatogenesis was observed, nor were changes in the interstitial tissues found.

"The preparation given to these animals was the same potent male hormone that is being widely used clinically, and in view of these negative results it is of interest that relative to their body weights some of the monkeys received much larger doses than are likely to be given in clinical practice, while others received low doses for long periods."

Action of Testosterone Propionate on the Female—As a consequence of both Zuckerman's experiments with twice-weekly injections of 25 mg. of testosterone propionate to rhesus monkeys over a period of 7 months, obtaining the inhibition of follicular maturation and luteinization and consequent suppression of menses, and of similar experiments with rabbits and rats which yielded like results, testosterone propionate has been used therapeutically for excessive and irregular uterine bleeding due to hyperfolliculinemia.

G L Foss²⁸ has used this treatment over a period of 18 months. His early results were variable, probably because of inadequate dosage. He reports 6

cases, and recounts his experience with some 16 cases.

The author finds that most patients require, according to the severity and duration of bleeding and the nature of the disorder, total doses of 300 to 800 mg. for inhibition of endometrial proliferation. In some cases of menorrhagia cyclical doses of 20 to 40 mg. administered twice weekly for a few months are sufficient to counteract follicular overaction, or to restore a cyclical rhythm in metrorrhagia. Severe cases need a total dose of 800 to 2000 mg. in daily injections of 100 mg., or in twice-weekly injections of 150 to 200 mg, the individual dosage being adjusted to the clinical history.

Just why testosterone propionate should have an action so antagonistic to that of estradiol is not known. It is in very close chemical relationship to estradiol, and can be made synthetically by complete hydrogenation of dihydroxyestrin or estradiol. Administration of testosterone propionate in a male gives rise to excretion of both androgen and estrogen in the urine.

Experimental and clinical work has proved that testosterone propionate injected into females counteracts the natural follicular hormone. This suggests 2 possibilities: (a) That the male hormone is a direct antagonist of the follicular hormone, and (b) that it inhibits anterior pituitary gonadotropic hormone. From experiments with rhesus monkeys, the latter hypothesis seems the more likely.

In the series of 16 cases treated during 9 months, doses up to 2200 mg were given in periods ranging from 3 to 8 weeks, and in all this series no unpleasant side effects were noticed. In those patients receiving intensive therapy for a short period or in those receiving moderate doses over a long period there

was a definite increase in size of the clitoris. This symptom cannot be considered unpleasant, since no patient complained of discomfort or swelling of the genitalia. It is not yet known whether the size of the clitoris decreases when therapy is discontinued.

The amenorrhea induced by testosterone propionate is of fairly short duration and the previous normal rhythm is restored when the injections are ended. In most cases the endometrium is in the resting stage and the glands are of the interval type; in no case has a secretory-phase endometrium been found.

In summarizing, the author states: Metrorrhagia and menorrhagia can as a rule be controlled by injection of testosterone propionate in adequate doses. The amount required depends on the clinical findings and the pathology of the condition. A temporary therapeutic menopause, with its associated symptoms, can be induced with large doses. Menstruation may be postponed for several months after treatment, ovulation and luteinization can be inhibited, and the endometrium is usually found to be in the resting stage. The breasts become smaller.

Only 2 cases proved refractory to treatment, even to large doses.

Action of Testosterone Propionate on the Uterus and Breast—A. A. Loeser²⁹ reports the results of therapy in 14 patients, 5 of whom were suffering with menorrhagia (10 to 14 days' loss at each period), due probably to small intramural fibromyomas, 5 with menorrhagia of unknown cause who reacted similarly to the therapy, 1 with metrorrhagia, and 2 with normal periods but suffering with chronic mastitis.

Since the pretherapeutic curettage performed on the first 5 patients produced no change in the menorrhagia, they were administered intramuscularly 50 mg. of

testosterone propionate on alternate days for 2 weeks or longer. A total dosage of about 300 mg. was found to postpone the period 8 to 10 days. This also made the menstrual flow scantier and of shorter duration, and 500 mg. caused complete suppression of the period. In 1 case so treated the curettage showed an atrophic endometrium. When treatment was continued the menstrual period did not return, and during this time the fibromyomas evidenced a distinct shrinkage, though they never actually disappeared. Menstruation recurred 6 to 10 weeks following discontinuance of therapy. One case of metrorrhagia reacted similarly to the therapy of 500 mg. over a period of 4 weeks.

The 2 patients with normal periods who suffered with chronic mastitis were favorably influenced by this therapy. As the mastitis disappeared, however, the endometrium became atrophic; the dosage required to cause the complete disappearance of the mastitis was 600 mg.

In general, 12 injections of 50 mg. or 6 injections of 100 mg. were administered within 3 or 4 weeks. No harm whatever was caused by these injections, even when given for 7 months up to a total of 1500 mg. Excellent results were obtained in 2 cases of dysmenorrhea with 150 mg. only.

NOTE—There have been reports of signs of virilism appearing in some cases, particularly in young women who have received large dosage of testosterone propionate.

Inhibition of Lactation During the Puerperium by Testosterone Propionate—R. Kurzrok and C. P. O'Connell³⁰ report their excellent results in 19 of 21 successive cases of early lactation during the puerperium which were treated with 50 to 150 mg. of testosterone propionate to inhibit lactation for various reasons.

The patients received 2 doses per day for 1 or more days, the injection being administered deep in the gluteal region. It was not unusual for doses of 25 mg. to obtain complete relief of all symptoms within a few hours of the second dose, which was generally administered 8 hours subsequent to the first dose. On the whole, 40 mg. or more of testosterone propionate were required to relieve all symptoms of breast engorgement. Complete relief of symptoms usually occurs within 48 hours.

The first case considered as unsuccessful had complete relief of symptoms on the fourth day. It may be argued that without treatment there would have been spontaneous relief by that day, yet on the other hand, an additional dose, beyond the 50 mg. administered, might have terminated the symptoms sooner. The other case received a total of 75 mg of testosterone propionate, the first dosage of 25 mg being administered on the first day post partum. The symptoms were not relieved. This case was the only one to receive the treatment on the first day post partum, and as the milk generally "comes in" on the fourth day post partum the inhibitory effect of testosterone propionate may have been exerted a little too early.

In all cases but 1, once the symptoms were relieved there was no tendency towards their recurrence after treatment had been stopped. The best results were obtained with doses of 25 mg each. There were no unpleasant side effects from the treatment, and the onset of the first menstrual period was not delayed.

Testosterone Propionate in Hypogonadism—S. A. Vest, Jr., and J. E. Howard³¹ report their results with testosterone propionate therapy in 6 cases of hypogonadism and 2 cases of prepubertal boys.

The 6 patients reported in this study are well past the normal age period of adolescence, their ages ranging from 22 to 62. They appear to divide into 2 groups: (a) Primary testicular insufficiency due to castration, atrophy following trauma, or an inherent defect in the testes themselves, 5 cases; and (b) gonadal insufficiency secondary to demonstrable pituitary disease, 1 case.

The authors agree that in man libido and potentia are highly complex functions, with psychological, neurological and hormonal factors closely integrated, but admit that just what rôle the sex hormones play is not yet fully understood. While concurring with other authors that caution must be employed when interpreting subjective improvement of libido and potentia as proofs of hormonal effects from hormone therapy, they nevertheless feel warranted in stating that in at least 2 of their cases the return of libido and potentia, long absent, was almost certainly due to the injected hormone. The rapid development of masturbation in the younger juvenile case treated offers further subjective evidence of increased libido resulting from injected hormone.

The subjective evidence in the other patients may be somewhat debatable, although there was increased libido and potentia in all cases. Seminal emissions were induced for the first time in 3 of the hypogonad cases, and greatly increased in the fourth. There was evidence of general improvement, both psychic and physical. There were also noteworthy gains in weight, from 10 to 25 pounds.

The objective changes in the patients are more easily evaluated. As regards the growth and development of the genitalia in the patients, the authors feel the proportionate developments in the phallus, scrotum, prostate and seminal

vesicles to have been within the limits of normal variation, that is, they did not note the testosterone to have stimulated any of the accessory organs either more nor less than would occur under the stimulus of normal development. Further, no disproportion was noted in the juvenile cases.

In several cases there were striking skin changes. In 4 patients whose skin had been dry before treatment, the skin became more, or very much more, oily. With the increased sebaceous secretion there also appeared acne vulgaris in 3 of the 4 patients, in 2 of whom it persisted. All 4 patients with hypogonadism showed increased hair in the axillae, on the extremities and on the pubis while under treatment. The beard growth, however, has not as yet been significantly increased. One of these patients further noted a change in pitch of the voice at the end of 7 weeks' treatment.

A definite increase in the size of the testes has been noted in the 4 patients with hypogonadism. The 2 juvenile cases, aged 4½ and 9 years, were treated for 18 and 4 months respectively, during which time there was no change in testicular measurements. But there has been an appreciable increase in the size of the testes following discontinuance of therapy, in the younger child, after the third month, and in the elder, during the subsequent 10 months.

The effect of testosterone propionate on spermatogenesis was studied in only 1 patient. Prior to treatment the expressed seminal secretion showed a few nonmotile spermatozoa. At the end of a year's treatment, there were observed numerous spermatozoa with 20 per cent actively motile, and all were of normal size and configuration. Moreover, the patient's wife became pregnant during the tenth month of treatment for the first time in 6 years of marriage. There

was a miscarriage, but the fetus appeared grossly normal. In the other patients of the series, including the juveniles, the expressed seminal secretion has shown no spermatozoa.

The dosage of testosterone propionate necessary to maintain the effects noted is difficult of evaluation. The dosage has varied from 5 mg. 3 times a week for 1 month, with return of libido after the second week, to 25 mg. daily for about 10 weeks. The average dose was 25 mg. 2 or 3 times weekly, and maintenance dosage, about 25 to 50 mg. per week. There may be subjective manifestations on stopping therapy, occurring from a few days to several weeks after. There has been no evidence in the patients of resistance or increasing tolerance to the hormone. No unpleasant reactions to the injections, either local or general, have been experienced.

In summary, the authors state, "testosterone propionate seems to be a satisfactory replacement therapy in the human. We have shown it produces profound anatomical changes resulting in the proportionate growth of the phallus, scrotum, seminal vesicles and prostate, as well as development of pubic, axillary and extremity hair. There have been laryngeal changes, the appearance of considerable prostatic secretion, and an ejaculum with coitus, and marked changes in the skin. There have been, in addition, changes in the general appearance, with improvement in the personality content. It has induced libido and potentia in individuals in whom these had not existed previously, and restored normal sex life in a patient who was impotent following castration. No evidence of increase in tolerance to the drug has been noted."

Male Sterility

Treatment—N. J. Heckel¹³² reports his results in 20 sterile male patients who

had azoospermia, oligospermia, or necrospermia, treated with the *gonadotropic principle* (*antuitrin*, 25 R. U. per cc.) and the *extract of pregnancy urine* (*antuitrin-S*, 100 R. U. per cc.). The condition was discovered in examining the spermatozoa, a procedure undertaken of necessity, either because of a sterile marriage or because the marriage had had no pregnancy for several years.

The patients selected were those in whom there was no apparent cause for sterility or in whom the sterility was due to a unilateral or bilateral testicular atrophy. Following 4 or 5 days' abstinence from sexual intercourse, the ejaculation was collected directly in a glass container, and after liquefaction had occurred, usually 15 or 20 minutes later, it was examined.

The first group of patients, treated with the gonadotropic principle, was composed of 12 married men between the ages of 27 and 40 years. Two pregnancies resulted, 1 in a sterile marriage of 3 years, and the other in a marriage in which 4 years had elapsed since the last pregnancy. In the first case, aged 27, with a diagnosis of oligospermia, the initial spermatozoa count was 4,600,000 per cc. After daily injections of antuitrin over a 7-month period, the spermatozoa count had gradually increased to a maximum of 26,000,000 per cc. His wife had become pregnant during the fourth month of treatment. The second case, aged 35, with marked oligospermia, received 800 R. U. of antuitrin over a 4-month period. The spermatozoa count gradually increased to 80,000,000 per cc. His wife became pregnant during the third month of treatment.

The 10 cases in which no pregnancies occurred were divided into 3 groups: (1) Two had azoospermia, 1 from an undetermined cause, the other from bilateral testicular atrophy following mumps

No change occurred after they had received 1700 R. U. in 8 weeks, and 1175 R. U. in 10 weeks, respectively. (2) Three had oligospermia, with less than 100,000 per cc. before treatment. There was no change in their conditions after they had received 6475 R. U. in 20 weeks, 5050 R. U. in 20 weeks, and 2850 R. U. in 14 weeks, respectively. (3) Five had an oligospermia, whose individual responses varied greatly, as follows: (a) Age 32, with azoospermia. A total dosage of 14,050 R. U. After 20 weeks' treatment the spermatozoa count reached 2,800,000 per cc. with 25 per cent alive; after 9 months' treatment, 2,000,000 per cc. with 50 per cent alive and after 11 months' treatment, there was again azoospermia. (b) Age 37, with oligospermia (atrophic left testicle). A total dosage of 7362 R. U. The initial count of spermatozoa was 16,000,000 per cc. with 50 per cent alive, which, after 4 months' treatment reached 72,400,000 with 95 per cent alive, decreased the next month to 48,000,000 per cc. with 95 per cent alive, and decreased to half this count with 95 per cent alive, 3 months following discontinuance of treatment. (c) Age 31, with oligospermia. A total dosage of 3350 R. U. The initial count of spermatozoa, 18,000,000 all dead, reached 32,000,000 with 90 per cent alive after 6 weeks' treatment. At the end of 3 months' treatment this had decreased to 10,000,000 per cc. with 95 per cent alive. (d) Age 30, with oligospermia. A total dosage of 5075 R. U. The initial spermatozoa count was 15,000,000 per cc. with 75 per cent alive, which increased to 16,000,000 per cc. with only 25 per cent alive after 3 months' treatment, and decreased to 9,200,000 per cc. with all dead after 5 months' treatment. Following 6 weeks without treatment, the count had declined to 2,600,000 per cc., all dead. (e) Age

29, with oligospermia. The first series of injections totaled 4850 R. U. From an occasional dead sperm in H P F the count increased to 30 active sperm after 6 months' treatment, decreasing to 3 to 4 alive in H. P. F. during the following 3 weeks. Three months after discontinuing treatment, the count was 8,400,000 per cc with 65 per cent alive, but dropped to one-fourteenth this count, with all dead, 2 months later. On resuming treatment, the total dosage of the second series was 6650 R. U. The best result was $3\frac{3}{4}$ months later, when the count was 17,600,000 per cc. with 90 per cent alive, and of good motility. This dropped to 1,600,000 with 90 per cent alive but many deformed, after 5 months' treatment

The second group of patients, treated with the extract of pregnancy urine, was composed of 8 married men from 27 to 38 years of age. Two pregnancies resulted, both in marriages which had been sterile for 2 years. Of these, the first case, aged 32, received a total dosage of 13,600 R. U. in a 6-month period, by which time the spermatozoa count had risen from a few dead in H P F to a maximum of 75,000,000 per cc. His wife became pregnant in the eighth month of treatment. At the end of a year's treatment the count was only 10,000,000 per cc. The second case, aged 38, had oligospermia and an atrophic left testicle following mumps. At the end of 6 months the total dosage was 19,900 R. U., and the spermatozoa count had risen from 5 dead in H P F to 144,000,000 per cc. with 95 per cent alive. His wife became pregnant in the eighth month of treatment.

The 6 cases in which no pregnancies occurred were divided into 2 groups. (1) Three had atrophied testicles following mumps, 1 bilateral, and 2 unilateral, all had azoospermia. They received 3300 R.

U. in 10 weeks, 2400 R. U. in 6 weeks, and 3300 R. U. in 10 weeks, respectively. No change resulted from the treatment. (2) Three had marked oligospermia of undetermined cause. (a) Age 33. From an initial few dead sperm in H P. F. the count reached 19,000,000 per cc. with 90 per cent alive at the end of 16 months' treatment, on a total dosage of 39,000 R. U. (b) Age 29, with oligospermia. There was no change after 6 months' treatment on a total dosage of 11,000 R. U. (c) Age 31. From an initial spermatozoa count of 1,600,000 per cc with 2 alive and of sluggish motility, the count increased to 4,000,000 per cc with 50 per cent alive at the end of 1 month's treatment, on a total dosage of 3200 R. U.

In summary, the gonadotropic principle and the extract of pregnancy urine appear to influence the number and viability of spermatozoa where there is a disturbance in spermatogenesis, the efficacy of the 2 hormones appearing equal. In some patients, however, the phenomena are only temporary. Moreover, there appears an optimum period of spermatogenesis in patients who have been under treatment for as long as a year with the gonadotropic principle. Further treatment after this period causes a decline in the number of spermatozoa. It is of interest, also, that whereas the anterior pituitary-like principle has been observed to cause growth of the external genitalia in boys of prepuberty age, no similar growth response occurred in the male adults reported.

Benign Prostatic Hyperplasia

Hormonal Treatment—H. W. E. Walther and R. M. Willoughby³³ point out that prostatic hyperplasia has now to be regarded as an independent entity, although remaining inseparably bound up with endocrine changes affecting the

hypophysis and gonads. They discuss their favorable results with hormonal therapy in 15 patients, between the ages of 75 and 46, 8 of whom presented symptoms of early prostatism complicated either by prostatitis or impending sexual impotency, 4 of whom had serious cardiac complications that made surgical relief appear inadvisable, and 3 of whom refused to undergo operation. They report 3 of the 15 cases, to illustrate their results with androstine or perandren (a testosterone propionate) injected intramuscularly, and supplemented by oral administration of androstine, from which therapy clinical improvement has been obtained during the past 2 years. Additional prostatic massage was given in many of the cases.

None of the patients had arrived at the stage of complete retention (with advanced fibrotic changes). In all 15 cases treated, the residual either greatly diminished or disappeared. Nocturia was the symptom to show the greatest improvement, and all patients experienced less difficulty in voiding. Great improvement was shown at the end of 1 month's therapy in 2 of the cases reported, the other showing marked improvement at the end of 2 weeks.

The therapeutic dosage contained the following: The tablets of androstine 0.075 Gm. of orchitic extract or 8 Gm. of fresh gland; the ampules of androstrine, 1.5 cc. of either the hydrosoluble, 0.06 Gm. or the liposoluble, 0.03 Gm. principles (which were given alternately); and the perandren, 5 mg. of synthetically prepared chemically pure testis hormone corresponding to 250 I. U. The 3 cases reported received 0.03 to 0.006 Gm. of androstine 3 times weekly for 2 to 3 months, this dose was later decreased to twice weekly injections in Case 3. The oral medication in Cases 1 and 2

(the other case not receiving any) was instituted 1 month after beginning treatment, and varied from 1 to 12 tablets daily, decreased to maintenance dosage of 8 to 12 weekly in Case 1; the other patient receiving 4 daily for 3 months.

It is not suggested that this form of therapy should ever replace surgery, but it should be allowed conscientious trial in cases of early prostatism or where some serious physical disability in any type of prostatic obstruction makes surgery inadvisable. It is, moreover, not claimed to produce permanent results, the symptoms having so far shown a tendency to recur or discontinuance of therapy. Therefore a maintenance dosage must be continued, necessitating contact with the patient for an indefinite period. Massage is usually indicated concomitantly with the extended medication.

Prognosis in Malignant Disease of the Testicle

R. T. Payne³⁴ reports a follow-up of 38 cases of malignant disease of the testicle, all of which were treated by means of orchidectomy with some receiving additional treatment from various forms of irradiation, wherein it was found that in no less than 15 (46.9 per cent.) of a possible 32 cases was there a cure rate of 5 years or over. In view of the disease being generally considered as uniformly fatal, a 5-year cure rate becomes encouraging.

In all cases there was pathological confirmation of the diagnosis. The orchidectomy was a local operation, and no patient was subjected to the radical operation. Subsequent to operation some patients received additional treatment including excision of inguinal glands, the insertion of radon to abdominal glands, and radiotherapy. The histological data revealed there were 19 teratomas, com-

prising also all tumors having a definitely mixed structure, and 19 seminomas, comprising also those previously described as alveolar sarcomas. There were no chorionepitheliomata in the series.

Of the 38 patients, 34 were traced. The deaths were 2 from operation and 14 from disease. The cures were 15 for 5 years and over (8 teratomas, 7 seminomas), 2 for 4 years (1 teratoma, 1 seminoma), and 1 for 3 years 5 months.

The theory that testicular tumors should be radiosensitive, is, in the case of secondary growths, supported by clinical evidence. Some form of irradiation, in addition to orchidectomy, was used in 15 of the 38 patients. This included **x-rays, deep x-rays**, and the use of **radon** in 1 patient (in aortic glands). The x-rays were employed sometimes therapeutically and at others prophylactically—so-called. Fairly high voltages were used, but Case 32 was the first of a series treated with deep x-rays.

The average duration of symptoms prior to operation was 7.5 months, and the time difference between those cases having a 5-year cure and those dying from the disease was 7.4 and 8.7 months—a period of 5 weeks. It becomes evident that the interval could, and should, be considerably reduced.

In diagnosis, a routine Wassermann test is essential in all cases, and the routine employment of the Asheim-Zondek test is advocated. A recurrence of the tumor in other sites may be recognized by the increase of prolan A in the urine. A high excretion of this may also indicate a hyperplasia of the prostate and seminal vesicles. Gynecomastia may also occur.

The number of good results obtained by the combining of operation and irradiation suggest the double treatment to be of greater therapeutic value than either method used alone.

THE THYROID

Testicular Deficiency Due to Hypothyroidism

E. P. McCullagh³⁵ reports a case of hypogonadism wherein is apparently illustrated the relationship, first, between the androgenic excretion and the hypogonadal symptoms, including impotency, and, second, between hypothyroidism and the androgenic excretion.

A white man, 50 years old, was first examined 3 years ago. Impotence had been slowly increasing, and libido had been disappearing over an 18-month period. For 6 months impotence had been almost complete, and no ejaculation had occurred under any circumstances. His strength and energy were fairly good, there was some irritability, but no other nervous symptoms. Adequate rest and vacations had brought no improvement.

He was an alert, apparently healthy man, 73 inches tall and weighing 166 pounds. His temperature was normal, his pulse rate varied between 65 and 80 beats per minute, his skin was only slightly dry and the color good. His blood pressure was 115 systolic and 80 diastolic. The prostatic secretion contained from 10 to 20 white blood cells per H. P. F. and appeared normal. The prostate and the genitalia were seemingly entirely normal.

A modified Friedman test gave a positive reaction with 4+ corpora lutea in the test animals. A later similar test gave entirely negative findings. An assay for urinary androgens, made previously to these, showed no comb growth in 2 birds tested. Later assays gave between 2 and 4 mm of comb growth, the normal by this method being 10 mm.

The diagnosis was functional hypogonadism. Injections of **testosterone**, 1 cc (25 mg of active material), were

given about 3 times a week for 5 months. Erections appeared at the end of 6 weeks' treatment for the first time in 3 or 4 months. No other change was noted, and no further improvement was noted by the next month. At the end of the 5 months a modified Friedman test gave 39 units of urinary androgens. There was at this time a slight improvement in the symptoms.

The next month the injections were changed. *Testosterone propionate*, 5 mg., was given 3 times weekly. At this time the B M R was minus 25. Within a few days there was a distinct increase in potency. The treatment was continued for about 6 weeks, 2 weeks without treatment inclusive. The specimen of the semen examined at the end of this series was 12 cc. in volume, and contained a spermatozoa count of 1,920,000, but of very slight motility and 20 per cent morphologically abnormal. The next week the dosage was increased to 10 mg 3 times weekly, and continued for about 4 months. At the end of this time the B M R was minus 15. Treatment was discontinued for 6 weeks, at the end of which time it was found the urinary androgens had declined from 65 to 26 I U to 10 I U. The preceding 4 weeks had found many of the symptoms returning, there was some paresthesia of the hands and feet, and the nails were rather brittle. There was relatively little impotence until the very end of this period, when it returned. Desiccated thyroid was given in dosage of 1 gram daily. The fatigue, mental dullness, and paresthesia which had appeared during the preceding 6 weeks disappeared promptly. The impotence disappeared almost completely, comparative to the reaction to testosterone propionate. Within about 4 months the B M R was minus 23 per cent, the androgenic excretion had increased to 45 I U. The dosage was increased

to 3 grains daily, and within 1 month the B. M. R. averaged minus 5 per cent. The patient was almost symptom-free.

In discussing the case, it first appeared to be one of testicular deficiency. The injections of testosterone propionate relieved the impotence when the dosage was sufficient to raise the urinary androgens to a range within normal. Discontinuance of therapy found the symptoms recurring. Subsequently there were distinct clinical manifestations of hypothyroidism. The thyroid therapy instituted obtained results equal to the hormonal treatment in high dosage. The improvement in the symptoms was associated with a distinct rise in the urinary androgens and disappearance of impotence.

The author considers this a case of hypothyroidism causing impotence by the production of a secondary testicular deficiency. He also points out that, as deduced from repeated assays, 25 mg. of testosterone propionate was excreted in 3 days, thereby suggesting a gauge for the frequency with which injections should be given.

Clinical Aspects of Hypothyroidism

C L Hartsock³⁶ presents an excellent comprehensive survey of the signs and symptoms of hypothyroidism, which, by reason of its unimpressiveness both in nature and in clinical characteristics, is very difficult of diagnosis, but whose cure is of relatively easy accomplishment.

A simple classification of the disease which serves also as the author's outline is as follows: (a) Myxedema, or severe hypothyroidism in adults, (b) cretinism or severe hypothyroidism in children, (c) postoperative or postradiation hypothyroidism and hypothyroidism as the result of exhaustion of the thyroid due to untreated hyperthyroidism. In this latter condition there may be symptoms

of both hypo- and hyperthyroid activity, hence its frequent name of "dysthyroidism," and (d) incipient hypothyroidism, which may be mild and atypical in patients of any age

The most obvious clinical sign of myxedema is a characteristic coarsening of the skin, especially of the face, eyelids, and the supraclavicular region of the neck, and other characteristic signs and symptoms are almost always present. In cases, then, where this edematous condition is absent, the better term would be "incipient hypothyroidism." The 2 types may differ only in degree, since the latter, if allowed to go too long unrecognized, will develop into the former. Because of this possibility, the author later offers a more definite picture of the "premyxedematous" stage

When actual myxedema is present, the thyroid deficiency is already marked and frequently of long standing. In general, the onset and progression of symptoms has been so gradual that the patient has been unaware of his subnormal health until the point is reached when the dulling of the mental faculties causes him to seek medical advice. In the advanced stage of the disease, the patient may complain of almost any symptom which can result from low metabolism. These symptoms have been known to be referable to every organ in the body, and all have been relieved by the administration of thyroid extract.

The physical examination reveals the temperature to be low, the skin dry and edematous, especially in the face, hands, feet, and supraclavicular fossae, the nails brittle and ridged, the pulse slow, and the blood pressure low, with the pulse pressure especially low. Albumin is often present in the urine, and there is almost always some anemia, occasionally so marked as to suggest pernicious

anemia. Free hydrochloric acid is frequently absent.

"Cretinism is the term applied to the marked retardation of physical and mental development produced in children by severe thyroid deficiency. This condition is frequently congenital and the retardation of development begins at birth, but rarely, except in the most marked cases, is it discovered until the child is found to be slow in the development of activities and normal functions. Even then, recognition of the condition is often delayed because characteristic appearance usually does not develop clearly until about the second year." Many of the symptoms are those of myxedema. "In milder cases cretinism must be differentiated from rickets, birth injury, mongolianism, dwarfism, and achondroplasia. Careful study will easily differentiate these conditions but, except for rickets, it is better to treat any of them with thyroid extract until the diagnosis is definitely determined, than to leave a case of cretinism untreated." Even those cases which are recognized early often receive inadequate treatment. Hence the author advises administering thyroid extract to the point of toxicity in order to determine the correct dosage.

While cretinism is not common in the goiter districts of the country, there are nevertheless sporadic cases. Their frequency is such as to necessitate vigilance on the physician's, and especially the pediatrician's, part. The children in these goiter districts very often have low grade cretinism that does not produce symptoms greatly suggestive of their true origin. Such cases correspond to incipient hypothyroidism without myxedema. A prophylactic treatment of goiter should be the administration of iodine to children and expectant mothers, which would also lessen the incidence of this condition. The author feels that better

standards for determining the B. M. R. in children would give great impetus toward the correction of these mild cases of hypothyroidism.

The prognosis in the severe cases of cretinism is poor as a result of the marked retardation which has probably occurred before the condition has been recognized. However, amazing changes do occur after a short period of treatment.

Hypothyroidism should be suspected in all cases again complaining of ill-health after having received some form of therapy for their previous hyperthyroidism. This is equally true when there has been spontaneous cure. It can be very difficult to diagnose when exophthalmos persists and no signs of myxedema are apparent.

There is often great reticence on the part of the patient to take adequate and prolonged treatment through fear of re-inducing hyperthyroidism.

Symptoms—The milder degrees of hypothyroidism are the most frequent, and incipient hypothyroidism is not only the most prevalent but the most difficult of diagnosis. In considering hypothyroidism as myxedema the physician occludes 75 per cent of the patients with some specific thyroid deficiency. The following is the list which the author has made of some of the more common signs and symptoms.

Central Nervous System—Somnolence is a sign the patient is in a myxedematous condition. Forgetfulness, lack of concentration, and a tendency to procrastinate are symptoms which appear in the late stages. Restlessness, nervousness, and insomnia are more common to the mild cases. Chronic headache which recurs frequently is also a common symptom. These symptoms are more the result of the general fatigue and

hypotension than the direct results of the metabolic disturbance.

Ocular System—Muscle errors which are due to fatigue of the ocular muscles are very common and these, in turn, may cause a host of vague secondary symptoms, such as dizziness, headache, neuralgia, and many others that are often ascribed to neurasthenia. Exophoria which occurs toward the end of the day is the most frequent type of muscle imbalance.

Ear, Nose, and Throat—A slight edema of the membranes of the nose and throat may be secondary to hypothyroidism. Allergy is usually more pronounced when it is associated with this condition. A very interesting symptom complex, the result of this edematous condition, of the membranes, is for the orifice of the eustachian tube to be swollen, with a tendency for the tube to close, so that the patient complains of the very annoying sensation in the ear from this closure. This sensation has a tendency to disappear and recur several times in the day. Several measures may relieve this condition temporarily, but adequate thyroid treatment will give quick and permanent relief. Tinnitus is sometimes due to the same cause. Degeneration of the eighth nerve should be suspected of being due to thyroid deficiency. Swelling of the tongue and chronic hoarseness are late symptoms of myxedema.

Cardiovascular System—Bradycardia should always suggest the presence of hypothyroidism but the pulse rate is an unreliable guide because in many cases it is normal or increased. Occasionally thyroid deficiency is the sole explanation for myocardial weakness. Dyspnea is entirely a secondary symptom. Occasionally the particular sighing type of dyspnea may be due to hypothyroidism.

Gastrointestinal System—Obstinate constipation is a characteristic symptom, but all types of indigestion due to fatigue of the gastrointestinal tract may be caused or aggravated by the disease. Achlorhydria seems to occur somewhat more frequently in hypothyroidism, but adequate therapy certainly does not cause a return of the hydrochloric acid.

Genitourinary System—One of the classical errors in diagnosis is mistaking a case of myxedema for nephritis because of the large amounts of albumin in the urine. Impotence and sterility both in the male and female should cause hypothyroidism to be suspected. (A woman who had been unable to carry pregnancies to full term had 2 full-term, normal pregnancies after thyroid therapy had been instituted.)

Glandular System—Polyglandular disturbances associated with hypothyroidism as a minor or secondary feature are very commonly found, but in many cases the entire glandular syndrome is improved by the use of thyroid therapy alone, and this is especially true in ovarian types of menstrual disorders. It is also of great value in the treatment of pituitary, thyroid, and ovarian types of polyglandular disorders in conjunction with other indicated hormonal therapy.

Skeletal and Muscular System—Vague muscular aches and pains frequently have their origin in thyroid deficiency. Any tendency toward degenerative arthritis is hastened by a low metabolic state. The disturbance of skeletal growth is exemplified in the cretin.

Hematopoietic System—A mild hypochromic anemia without any other satisfactory explanation should arouse suspicion of thyroid deficiency.

Hair, Nails, and Skin—Dryness of the hair, brittle and thick, coarse nails, falling hair, and premature graying of

the hair are very suggestive symptoms of this disease and sometimes give the earliest clues.

General Symptoms—Obesity, both generalized and that localized around the pelvic and shoulder regions, is the classical sign which usually directs attention to hypothyroidism; however, a fact not so well known is that many thin individuals who never could gain weight begin to do so immediately when they follow correct treatment for mild thyroid deficiency. Localized and circumscribed swellings are frequently of myxedematous origin. Swelling of the extremities with changes of temperature or prolonged dependency suggest an early myxedema. Intolerance to cold and a subnormal temperature is usually found, but several cases of chronic pyrexia have been reported that responded to no therapy other than thyroid. Lack of thirst and hypohidrosis are further suggestive general symptoms. Many other vague symptoms could be cited that are secondary to the chronic fatigue, decreased cellular function, and inadequate oxidation of thyroid insufficiency, but this would only confuse the picture.

The variation in the picture of hypothyroidism in patients in the different age groups is also confusing. Diagnosis of the milder forms of the disease is extremely difficult for various reasons which the author outlines. Severe hypothyroidism can be present in middle-aged patients with surprisingly few of the classical symptoms. Patients in this group present at least a few of the symptoms suggestive of the clinical picture of myxedema; rarely do they show all of them.

Differential Diagnosis—The symptomatology of the clinical syndrome, achlorhydric anemia or idiopathic hypochromic anemia, frequently suggests hypothyroidism and, unless laboratory

studies clearly differentiate the 2, it is sometimes necessary to determine whether iron or thyroid replacement therapy is the more specific before the true diagnosis can be determined. Some cases are apparently a combination of both conditions and these do better when both medications are used.

Any asthenic state may be confused with the hypothyroid state until a therapeutic trial proves or disproves the relation of the asthenia to a deficiency of thyroid. Only by a therapeutic trial can many such conditions be differentiated. There is, however, one very common clinical syndrome that is mistaken most often for hypothyroidism, namely, the depressed states described under various terms such as melancholia, nervous exhaustion, manic depressive-cyclothymia, involutional melancholia, cerebral arterial sclerosis, and many others. These cases do not respond to thyroid medication.

Obesity more than any other sign is suggestive of hypothyroidism, and due to the difficulties of calculating accurate B. M. R., some types of obesities are falsely treated for hypothyroidism.

Treatment—The widespread fear of thyroid medication is the greatest handicap in the treatment, says the author. While it is true that symptoms of hyperthyroidism can be quickly induced, these symptoms subside as quickly when the medication is stopped. A patient should be seen often until the correct dosage is established, and the author advises that this be achieved through giving small doses, increasing them until a point of mild toxemia is evidenced, and establishing the dosage just below it, where no such symptoms are manifested. This including of slight toxemia from which to gauge adequate dosage is advocated because so many patients under treatment for thyroid deficiency do not receive their maximum tolerance.

Several points emphasized are, the use of small doses on beginning therapy, and the familiarization of the physician with the therapeutic properties of a very few thyroid extracts, together with the action of thyroxin, as the first will enable more satisfactory results, and the second will prove of benefit in those cases which do not respond to thyroid extracts, the reverse also being true. Further, the maintenance of adequate dosage even after the B. M. R. has been raised to within normal levels, as it must be borne in mind the therapy is one of replacement and so may have to be continued throughout the patient's life.

The dosage also is dependent at times on the temperature of the weather, since more thyroid is needed during cold weather. Less dosage is required when the patient is sojourning any length of time at the seashore. Much fresh seafood in the diet is advocated, but iodine is not given in conjunction with the thyroid treatment. During the early part of the therapy a B. M. R. should be done monthly, and the symptoms of the patient should be checked weekly. The medication should be given in the earlier part of the day, since if taken as late as 6 hours prior to bedtime, there may be palpitation on assuming the recumbent position. Moreover, the subnormal symptoms are more pronounced in the morning.

Also, a therapeutic test for short periods in doubtful cases often yields, says the author, brilliant diagnostic and therapeutic results in an otherwise puzzling case.

Hyperinsulinism Associated with Hypothyroidism

J. L. Carmichael²⁷ reports 2 cases of hyperinsulinism associated with hypothyroidism which were treated with 3 grams

and 4 and 5 grams of *desiccated thyroid* respectively, with results that suggest the increased utilization of thyroid secretion in the body depressed the production of insulin so that the blood sugar remained at a higher level and thereby prevented further convulsions in Case 1, and reduced their incidence in Case 2.

The first case was a white man, aged 36, who had had a convulsion, following which he had remained unconscious for 30 minutes. The physical examination revealed a well-developed and well-nourished young man in whom there was apparently nothing abnormal, with the exception of the swollen and lacerated tongue. Pupils were equal and symmetrical and responded to light. The reflexes were normal. There was nothing significant in his past history other than that he had awakened several weeks previously with a sore and swollen tongue, and that he had at times great difficulty in keeping awake.

Laboratory examinations were negative. A spinal puncture revealed the fluid to be under normal pressure. There were 7 cells per cc and a trace of globulin. A fasting blood sugar determination was 108 mg per 100 cc of blood, and a redetermination gave it at 87 mg. A B M R taken immediately before a glucose tolerance test was done gave, in 2 tests minus 15 each time. The glucose tolerance test readings, taken at the end of every hour gave (from a fasting blood sugar of 87 mg) 137, 120, 68, and 42. The therapy instituted was 3 grams of desiccated thyroid, daily, with resting periods, continued for $4\frac{1}{2}$ months. A B M R taken at this time showed a plus 3.6. The glucose tolerance test repeated also at this time gave hourly (from a fasting blood sugar of 87 mg) 127, 77, 80, 75. The blood sugar had remained higher and thereby prevented further convulsions. To date

the patient has had no recurrence of convulsion.

The second case was a white man, aged 39, who was suffering from recurring attacks of convulsive seizure and attendant loss of consciousness. He also complained of marked loss of memory of recent events. His past history and family history was irrelevant. The physical examination showed a well-developed, very overweight man, with no abnormal findings. His fasting blood sugar was normal, although the B. M. R. was minus 20. The glucose tolerance test with 100 Gm of glucose gave hourly (from a fasting blood sugar of 85 mg) 128, 112, 55, 56 mg. The low 55 mg occurred 3 hours after ingestion.

The patient was then administered 4 grains thyroid daily. A B M R, done less than a month later gave minus 3.8. The glucose tolerance test, repeated at this time also, gave hourly (from a fasting blood sugar of 92 mg) 174, 124, 84, 80, 88, and 92 mg per 100 cc. of blood. Because the patient continued to have occasional attacks, the thyroid dosage was raised to 5 grains daily. Another B M R done 3 weeks later showed a plus 7.5. The glucose tolerance test at this time gave hourly (from a fasting blood sugar of 92 mg) 184, 141, 95, 65, 78, and 90 mg per 100 cc. of blood. Despite this change in glucose tolerance the patient still continued having occasional attacks of the same convulsive seizures. His diet was investigated and was found to be indiscreet. He was therefore placed on a high fat and low carbohydrate diet. A follow-up reveals he is still subject to occasional attacks.

The author cites an indication of mutual antagonism existing between the thyroid and islet secretions, but he points out that no attempt has been made to determine whether the antagonism is

direct or through the intermediary of some gland, such as the pituitary. Further, he advocates trial of the therapy over a more extended period in order to permit trustworthy conclusions.

Hyperthyroidism

Medical Treatment with a High Fat Diet—S. Soskin and I. A. Mirsky³⁸ report a case presenting acute and severe hyperthyroidism who was of necessity treated with a high fat diet, since she absolutely refused to undergo the advised thyroidectomy, and the striking and complete recovery resulting therefrom.

The patient was a white woman, aged 36, with the symptoms and signs of severe hyperthyroidism. There was nothing significant in her history until the onset of the present illness 4 months prior to examination. During this 4-month period she had noticed nervousness and irritability, increased perspiration and tremor of the hands. The symptoms progressed, and added to them were increasingly frequent attacks of substernal pain. Physical exertion was accompanied by dyspnea and occasionally by swelling of the ankles. There had also been a loss of 14 pounds.

Examination showed some increase in the width of the palpebral fissures but no exophthalmos. There was a definite lid lag but no other eye signs. The thyroid was diffusely enlarged and smooth in consistency. There were no abnormalities in the respiratory system or abdomen. The heart rhythm was regular and there were no adventitious sounds. The blood pressure was 148 systolic, 74 diastolic. The deep reflexes were slightly hyperactive. The chemical examination of the blood revealed sugar 89 mg per 100 cc, total cholesterol 176 mg and cholesterol esters 123 mg. The electrocardiogram findings suggested a myocardial involvement. Three B M R

done every 3 days gave a plus 62.9, plus 53.3, and plus 55.2.

The diet followed while control data was being obtained was protein, 80 Gm.; fat, 80 Gm.; and carbohydrates, 400 Gm., giving a total calorie value of 2640. The therapeutic diet followed was protein, 90 Gm.; fat, 230 Gm.; carbohydrates, 90 Gm., giving a total calorie value of 2790. For 23 days this diet was increased with 3 Gm. of cholesterol daily. Rest in bed was enforced. There was no other form of therapy employed.

There was a gradual regression of all symptoms and signs from the time the therapeutic diet was instituted. The additional cholesterol did not appear to affect the rate of improvement, so it was discontinued. The almost daily attacks of substernal pain gradually became more intermittent, and ceased after 2 weeks on the diet. Two months later the B M R varied around plus 30. The blood pressure was 130 systolic, 80 diastolic; weight had increased 6½ pounds.

The patient has continued the diet, and after nearly 2 years she is perfectly well and able to undertake all normal activity. Her B M R. has varied around 0, 0, and her blood cholesterol has remained above 200 mg per 100 cc. for many months. Interpretation of the electrocardiogram shows it to be within normal limits. Her weight has remained constantly about 130 pounds (111½ to 118 to 130).

The authors do not propose the routine employment of this diet in place of the established surgery, but suggest its value in cases where operative measures are refused or where such measures entail too great hazards.

Effect of Antithyrotropic Serum on the Action of Human Thyrotropic Hormone

C. L. Cope³⁹ reports his studies with thyrotropic hormone from human pituitary

tary glands and antithyrotropic serum prepared in rabbits, proceeding from the postulate. If Graves' disease is due to an excessive production of thyrotropic hormone, the injection of a serum having strongly antithyrotropic properties should be expected to produce diminution in the symptoms of hyperthyroidism, thereby becoming a valuable therapeutic method.

He found that the antithyrotropic serum, prepared in rabbits against ox thyrotropic hormone, will antagonize the action of this hormone, but has a negligible inhibitory effect on the action of thyrotropic hormone obtained in a similar manner from human pituitary glands. Hence, owing to this species' specificity it is unlikely that such serum will prove of therapeutic value in the human subject.

THYMUS

Status Lymphaticus

Alan Moncrieff⁴⁰ observed in 12 young children with a symptomatology apparently associated with enlargement of the thymus glands, as shown by x-ray examination of the thorax, who were treated with radiation to the thymus which caused a decrease in size of the gland and was followed in all but 1 case by a symptom-free period of a year or longer.

Of the 12 patients 10 were boys and 2 girls, a male sex dominance already noted by others. Symptoms had occurred before 4 months of age in all cases but one, in whom the "attacks" began at 3 years. The principal symptoms were stridor only (5 cases), syncope and dyspnea (3), head retraction, 1 also with syncope (2), cyanotic attacks (1), fits (1), and dyspnea (1). In 1 patient infantilism was also present. All

cases showed an enlarged thymus. Enlarged thymus was not a common chance finding in children examined for disease of the heart or lung. The author thinks that thymic stridor might explain some cases of so-called "congenital laryngeal stridor."

It is of importance, due to any exaggeration in the symptoms possibly proving fatal, that there be prompt recognition of the nature of less serious attacks and their immediate treatment by radiation of the thymus. While in these cases it was difficult to attribute the underlying cause of the symptoms solely to pressure, the alternative would have been to consider the excessive internal secretion from the thymus antagonistic to the cortical secretion of the adrenals. It was, however, deemed inadvisable to withhold radiation while experimenting with adrenal cortical hormone.

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GASTROENTEROLOGY

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CHRONIC ULCERATIVE COLITIS (THROMBO- ULCERATIVE COLITIS)

By J ARNOLD BARGEN, M D

Definition, Etiology and History—

Chronic ulcerative colitis (colitis gravis) is now widely believed to be an infectious disease of the large intestine. A clearer understanding of the condition specifically designated as chronic ulcerative colitis and the realization that there are many ulcerative inflammatory processes of the colon that in the present state of knowledge cannot reasonably be included under this designation have, however, focused the attention of more and more students of this disease on the hypothesis that it is of streptococcal origin

A few workers still hold that the condition may be the end stage of an infection by organisms of what used to be called the colon-dysentery group, and which now would include *Escherichia coli*, *Shigella dysenteriae* and *Shigella paradysenteriae*. Their belief is based on the finding of these microorganisms in a

few cases of ulcerative colonic disease, a slightly elevated concentration of antibodies of these organisms in the blood of a few patients and the therapeutic response of some of the patients to administration of antidyenteric serum. In a study of a large number of patients who have this disease and of another group of patients who have other types of intestinal disorder, including cancer of the colon, infectious granuloma, amebiasis and irritable colon, as well as in study of normal individuals, a similar elevation of the concentration of antibodies of these organisms has been found. Because of these findings, and because men who have held to this belief have selected their cases from regions where *Shigella dysenteriae* is prevalent, this hypothesis of causation would hardly seem tenable.

Another hypothesis of causation has as its basis the idea of infection by a variety

of organisms. The thought has been that many kinds of bacteria, under special conditions, may initiate the pathologic process and may be responsible, in some instances, for its continuance. Among the organisms so incriminated have been *Escherichia coli*, pneumococci, staphylococci and others. It has been suggested that the normal intestinal inhabitants assume virulence when bodily defense to infection becomes reduced. The same could be said about any infectious disease, but that would not necessarily permit incrimination of the bacteria present at the site of infection late in the course of the disease.

A third hypothesis of causation has been concerned with deficiency of vitamins, minerals and other substances. Studies of large numbers of cases would suggest that, when deficiencies occur, they are not primary but occur more as complications of the disease.

Another hypothesis of causation of this disease has been concerned with changes in bodily metabolism, such as occur in diabetes, goiter and similar diseases. Experimental evidence for this is lacking.

Others have explained the condition as a result of a residual infection following infection by amebae and other parasites. There is much to support the thought that when parasites occur in association with chronic ulcerative colitis, either 2 separate conditions are present, in which the parasites are causing only part of the symptoms, or they are only incidental intestinal inhabitants.³

That there is a phase of allergy in bodily infections cannot be gainsaid. That it plays an important rôle in some intestinal infections is also likely. Some have thought that it is basic in some forms of ulcerative colitis.⁴⁵

The most widespread view, and one that is supported by much experimental evidence, is that chronic ulcerative colitis

is an infectious disease, caused by a specific microorganism or by a group of microorganisms. The group of microorganisms is of the streptococcal variety and much evidence is at hand to suggest that a diplostreptococcal form of characteristic biologic and morphologic properties is at least 1 of the main instigators of the disease. In the light of present-day knowledge, such an organism must be considered the inciting factor in this disease. Whether the organism alone is responsible for the infection or whether its association with a filtrable virus is important has been a recent subject of discussion. Some have suggested that the toxin of this organism is alone capable of producing the disease. This thought has led to the search for a filtrable virus. So far, the fact that both the toxin and the organisms seem to play parts in the inception of the infection again would establish the importance of the presence of the diplostreptococcus.

All these observations serve to emphasize the importance of a suitable name for the disease now known as "chronic ulcerative colitis." The pathologic picture of the condition, as it is seen in the living and in the dead, has been adequately described. Its sigmoidoscopic picture is clear cut and the steps in its development have been carefully and repeatedly observed and recorded. Its inception seems to have the following sequence: Attack on the bowel through the blood stream by a microorganism or its toxin, resulting in multiple thrombosis of capillaries in the wall of the bowel, followed by tiny hemorrhagic infarcts; dissolution of these infarcts; formation of minute abscesses, and the appearance of the disease from the mucosal side as a granular, bleeding surface. Only cases presenting this pathologic picture should be given a name that represents what is now known as chronic ulcerative colitis.

But since this name readily allows the inclusion of other ulcerative conditions, a more suitable and more descriptive term should be found. To this end many names have been considered and cast aside. The fact that the streptococcus is found to play a part in the picture makes it desirable that this fact be taken into consideration in choosing such a name. However, when etiology is brought into a name, such a name may become cumbersome. A mere description of pathology should be adequate. The designation "thromboulcerative colitis" would be descriptive and clear cut and would tend to avoid falsely classifying other conditions with this disease.

In an article by Cave and Mackie in April, 1938, appears this amazing statement: "It seems unusual that relatively little has been written about this disorder, the etiology being unknown, the course usually debilitating and prolonged and the outcome fatal to many." There are few subjects in medicine that have been more thoroughly and more generally discussed during the last 2 decades than chronic ulcerative colitis and this review, which cites 69 articles, covers only the years 1937 and most of 1938. Not all of the articles of the latter months of 1938 were available. A very thorough review of the subject for recent years occurs in a report by Moltke.⁴⁹ His bibliography covers 2 closely typed pages in very small print. He adds 125 cases to those previously reported.

Under etiology a large series of papers brought confirmatory evidence to the streptococcal hypothesis of causation.^{18, 26, 31, 33, 35, 37, 41, 42, 49, 50} Several reports concerned themselves with the relationship of thromboulcerative colitis to bacillary dysentery.^{13, 51} Further discussion of the relation of *Bacterium necrophorum* occurred.^{28, 29} Two papers on the relation of the virus of venereal

lymphogranuloma were injected.^{52, 63} The metabolic phases of the condition were mentioned.^{58, 67} The relation of upper respiratory infections to its inception was stressed.⁴² Its familial occurrence was noted.⁴⁸ Czabafy has been impressed with the association of thrombopenia in some cases of ulcerative colitis and he raises the question whether the usual streptococci of the intestine might not be responsible for both the thrombopenia and the ulcerative disease, the organisms assuming virulence under certain conditions of the individual.

The life history of patients with chronic ulcerative colitis of the streptococcal variety has been thoroughly studied.^{7, 64, 68} It has been pointed out that the vast majority of patients with this disease may get well in the sense that they become free of symptoms of the disease, providing they follow certain well-established rules of activity and living. Of 1 series of 871 patients, 71 per cent were either well or able to carry on in the capacity in which they had lived before they had the disease between 7 and 14 years after their first observation. Only 17 per cent of this series of patients had died and that included deaths from all causes, not only those from ulcerative colitis or its complications.⁷

Blood Picture—A distinctive blood picture is noted in most cases of chronic ulcerative colitis. There is present a hemoglobin-deficiency type of anemia, a marked shift to the left (Schilling) in spite of a normal total leukocyte count and a greatly increased sedimentation rate of the red blood cells.⁴

Complications—The complications occurring with this devastating disease are ever creating interest. Hepatic insufficiency has been noted, although its relatively rare occurrence has been worthy of comment.^{15, 17, 24} Although the occurrence of appendicitis and its

management in these cases has frequently presented itself, this problem has again been emphasized.⁶⁵ Attention has again been called to the occurrence of intestinal perforation followed by pneumoperitoneum⁷⁴ and by intraperitoneal hemorrhage.¹⁴

The care of the secondary symptoms and signs of deficiency late in this disease have been stressed^{16, 22, 38} The condition of pyoderma is always of interest in these cases.²⁵ The difficulty of differentiating between some of these cases and tuberculosis of the intestine is worthy of comment.⁵¹

Treatment—Among the therapeutic advances made in the management of chronic ulcerative colitis in recent years or the things that have been tried with seeming benefit, the following seem worthy of mention. Emphasis has been laid on the general depletion of these patients. With it there will occur evidence of vitamin deficiency late in the disease and the need of *vitamin A* has been emphasized.^{41, 59} Instillations of *cod-liver oil* into the rectum have been advocated as a source for this as well as to produce smoother healing of the rectal lining.^{9, 46, 62} Two ounces of warm oil may be instilled. Excessive hemorrhagic tendencies have been controlled by the administration of *vitamin C*.⁶⁰ Additional suggestions for materials to instill into the rectum are made from time to time. *Aluminum hydroxide* and *kaolin* have recently been advocated.³⁰ Elimination of foods to which patients might be allergic has been stressed.⁴⁴ Artificial fever therapy has been tried,³² but the cumbersomeness of the method and its exhausting effect will hardly make it a popular form of treatment. *Instillation of oxygen* into the colon has been suggested.^{27, 34} *Inhalation of oxygen* by the Boothby-Bulbulian-Lovellace¹¹ method has been shown to have

value⁵ for very ill patients or for those suffering from sepsis or toxemia. Finally, the use of *sulfanilamide* and the *sulfamido group of drugs* has found favor.^{2, 23} The former, however, has been found too toxic for use in most patients with this disease. More particularly, *neoprontosil* has found a definite place in the treatment of some of the cases of chronic ulcerative colitis.¹²

Cave and Mackie state that "up until the last decade surgery has played a minor rôle in the treatment of this disease. It is generally known that up until the last decade, operation, and particularly ileostomy, cecostomy and appendicostomy was a favored treatment. The trend has been steadily away from surgical treatment except for complications. Feder reviewed the records of 88 cases studied at the Beth-El Hospital and only 3 of them were operated on. Two of the 3 died."¹¹ *Ileostomy* and *colectomy*, and *ileosigmoidostomy* for the right-sided form of ulcerative colitis, have proved the treatment of choice in selected cases.^{8, 19, 20, 47, 50, 61}

Indications for surgical intervention of any type whatsoever will not occur in more than 15 per cent of all cases of this disease.¹⁹ and this will include those cases in which drainage of abscesses, operation on an occasional empyema of the gall bladder and the like have occurred.⁶ The trend has been definitely and steadily away from surgical treatment of this devastating disease. Improvements in medical care have occurred from year to year. A series of articles may be mentioned in this regard.^{1, 10, 36, 39, 40, 55, 56, 57, 60, 69} A review of the literature in the United States and other countries indicates the trend toward a more profound understanding and better care of patients suffering from thrombo-ulcerative colitis.

FUNCTIONAL DISORDERS OF THE COLON

By JOHANNES PESSEL, M.D.

There are still several schools regarding the cause and treatment of so-called functional disorders of the colon. Borsook⁷⁰ and his coworkers undertook a clinical study of 227 cases. They based their results on extensively detailed mimeographed questionnaires sent to the patients. One-quarter of their functional colon disorder cases improved as the result of a *well-balanced diet* and discontinuance of laxatives. They admit that other factors, particularly psychological influences, may play a tremendous part. The remainder, or greater number of their cases, were not influenced by the above, but were improved by large amounts of *vitamin B complex*, obtained from cereals or the branny coats of same. None of their cases showed any evidence of vitamin deficiency that they were able to prove.

All cases were studied from 3 months to 4 years. They conclude that marked benefit in nearly all cases resulted from continued ingestion of vitamin B complex, and that their results indicated a distinct vitamin B deficiency.

Alvarez⁷¹ attempted to prove an association of nicotine with functional disorders of the colon in the human, but concludes "I do not believe that we can connect nicotine in any way with the ordinary functional disorders of the colon in the human."

An interesting sidelight of the same subject is presented by Roy Kegerreis⁷² in a study of colon stasis and the effect of various types of cathartics. He advises that one should never use symptomatic improvement as a criterion: only x-ray evidence is accepted in the final analysis.

Wm. C. Menninger,⁷³ in a very instructive article on the functional disorders of the gastrointestinal tract, draws

a parallelism between the nature of diarrhea and psychological attitude toward life. According to this author, diarrhea is a substitute for giving something of real value, making a real effort, or being actually active. Also it is a method of expressing hate. Constipation has an equally psychological significance, namely to retain or hold out. The conscious attitude of these individuals includes a pessimism toward receiving help from others, or depending upon others. He advises *psychotherapy* for all. In the past most of this advice has been rather indefinite, and consequently the results have been very unsatisfactory. A careful anamnesis, a willingness to listen to details, absolute confidence of the patient; interest in vague situations, no matter how trivial they may seem; listening to the patient's fears, doubts, and troubles that exist in his life, either apparent or completely independent of the physical complaints, are absolute minimum requirements for success.

Psychotherapy also should include education or enlightenment about the gastrointestinal life, and the manner by which it can reflect the changes in the emotions of an individual. He advises that help of a psychiatrist be obtained. One must be guarded in the prescription of a regimen, mainly because if it is overemphasized or too rigid it adds to the patient's illusions.

Drugs should be prescribed only incidentally, or as a temporary crutch. They should always be used with care, because of the patient's tendency to capitalize upon them, thus solving a major problem of emotional disharmony.

The dietary recommendations also should be guarded, because so many become diet faddists, rather educate the

patient in dietary facts. He also advises physiotherapy as ideal in these individuals, because it can so readily be associated with suggestion.

Surgery is practically never indicated. He concludes: "From a psychiatric viewpoint, functional disorders of the gastrointestinal tract are primarily emotional in their causation. This fact is now granted by nearly everyone." The point is stressed that these individuals should have the benefit of an accurate and penetrating detailed analysis of the psychological components of their illnesses, and that only as we understand the dynamic aspects of the personality disorders can we adequately treat these individuals. The treatment in all cases must be directed toward the total personality, and not toward the intestinal tract.

Bond⁷⁴ has shown that patients with so-called "colitis" have been completely freed of their symptoms by a psychiatric analysis. He advises that every functional case should have his personality studied under these headings:

- 1 Early eating habits, or early attitudes toward family, schoolwork, etc.
- 2 Present-day emotional stresses and strains, frustrations, happiness and unhappiness, especially in marriage.
- 3 Does the patient make the gastrointestinal tract symbol of anything?

He quotes Adolph Myer as follows: "Often the gastrointestinal tract, with its receptive eliminative functions, can be that which expresses and leads the personality throughout life."

In a more extensive article, Wakefield and Mayo⁷⁵ graphically describe the disorder as mainly psychological, and feel that the etiological factor is intellectual and emotional. If the symptoms are due to unsuitable moral or religious tendencies, or a result of erroneous interpretations of defectiveness, disease, or supposed misconduct of the colon, recovery

may be obtained only through education. The patient's confidence must be gained. Under etiology, these workers place:

- 1 Systemic disease, as manifested by colonic symptoms, of such a degree that the underlying disease is masked

- 2 Environment, which creates social crises

- 3 Fear of disease, growing eventually sufficiently great to produce disability

- 4 Laxatives. The persistent use of laxatives may produce a mild functional disorder which will soon subside, but habitual use of purgatives may bring on psychological changes

- 5 Congenital faults

- 6 Other possible underlying causes as, allergy, irregular habits, excessive use of tobacco, coffee, or alcohol, lack of relaxation, insufficient vacations, and, finally, congenital mental and physical incapacities, and inherited nervous instability

Symptoms—The symptoms are constipation, diarrhea, at times alternating, varying amounts of mucus in movements, abdominal tenderness, general hypersensitivity to pressure, and gas. Often there are hyperactive reflexes, a tendency to fabrication, evasiveness, arrogance, irritability, and fixed, usually erroneous, ideas concerning the illness.

Diagnosis It is of importance that organic disease may exist or be superimposed on functional disorders of the colon. Therefore, a diagnosis should be made only after careful study, namely, repeated stool examinations, frequent sigmoid inspections, roentgenological study of the colon and terminal ileum by means of opaque enema, gastric analysis, endocrine studies, cutaneous allergy tests, blood and urine check for heavy metals.

Treatment—As treatment, these authors advise nonirritating bulk, such as *agar*, as laxatives; *educating the patient* that reactions are due to social crises, and that colonic discomforts are often reflex phenomena, and not the result of organic disease. They suggest few drugs, but *relaxation, rest, and allaying of all fears and anxieties,*

and a regimen which aims toward physical rehabilitation. *Colloidal clays, bismuth, dilute hydrochloric acid, and systemic sedatives* occasionally may be used. A *normal dietary regimen, heat to the abdomen*, and rectal instillations of *warm olive oil* may produce a distinctly gratifying effect. Surgical treatment is definitely contraindicated. If surgery becomes necessary, the patient must understand that it is not intended to alleviate the abdominal symptoms ref-

erable to the functional disease. In summary they state: "To eliminate these disorders, the defects in education, government, religion, morality, philanthropy, and even physical heredity must be corrected. This ideal may be approached when there is a scientific understanding of the conditions necessary for normal social life; never by treating these patients for 'colitis.' In conclusion, the wisest measures should be directed toward the prevention of these disorders."

CHRONIC GASTRITIS

By WILLIAM A. SWALM, M.D., and LESTER M. MORRISON, M.D.

The accumulating literature for 1938 on the subject of chronic gastritis testifies to the fact that the subject of chronic gastritis is arousing increased interest both in this country and abroad. Credit for the present appreciation of the clinical importance of chronic gastritis belongs directly to the researches of Knud Faber,⁵⁵ who first brought the modern concept of chronic gastritis before the profession in 1898. Due to the development of the semiflexible gastroscope by George Wolf and Rudolph Schindler direct gastroscopic observations of the stomach with chronic gastritis continues to grow. Of interest in 1938 contributions are numerous facts which are corroborative of previous and original observations, including many interesting case reports. Due to lack of space these reports must perforce be omitted from discussion here.

Etiology—Etiologically, the authors⁵⁶ confirm the belief of Faber and Hurst that chronic gastritis is one of the predisposers to cancer and ulcer of the stomach, in the sense that it prepares the "soil" (gastric mucosa) for the subsequent implantation of these diseases. They agree

with Schindler in that numerous patients with chronic gastritis complain of tenderness and pain in the area directly over the gastric silhouette. A neurogenic etiology is believed to be responsible for some of these cases of chronic gastritis, just as in peptic ulcer.

Incidence—The observations regarding the character and incidence of gastritis in different countries by May⁵⁷ is very pertinent. In regard to the controversy as to whether peptic ulcers and gastritis vary in different countries, which fact is denied by Walters⁵⁸ of the Mayo Clinic, May believes that from his surgical experience in both Germany and the United States there is a definite difference—a geometrical one in gastritis as well as ulcer—in both these countries. This corroborates the original belief in this fact held by Swalm, Jackson and Morrison.⁵⁹ May presents histologic sections as evidence of the fact that chronic erosive gastritis is more frequent than previously believed.

Diagnosis—Gauthier and Borland⁶⁰ emphasize the fact that secretory studies are of no avail in the diagnosis of gastritis. They believe that Schindler's

classification of gastritis, *i. e.*, superficial, hypertrophic and atrophic, are the most satisfactory and can be diagnosed only gastroscopically. These authors also believe that there is a common occurrence of peptic ulcer with gastritis as has been found before, and that these 2 conditions are separate and distinct entities.

Brown and Priestley⁹¹ report an interesting case of massive and recurrent gastrointestinal hemorrhage from a diverticulum with chronic gastritis. These authors believe that the hemorrhage was due to the gastritis. Comfort⁹² states that inflammatory processes which involve the mucosa of the stomach, as in chronic gastritis, can be responsible for the decrease of acidity of the gastric contents. He cites a case to support the belief that chronic gastritis can be responsible for the depression of gastric acidity that develops with increasing age.

Stocker⁹³ reiterates the now accepted fact that the x-ray diagnosis of gastritis usually is not possible, although it can be made in the hypertrophic and certain other forms. The gastroscope is the only reliable and direct diagnostic method in chronic gastritis.

Persson⁹⁴ has again called attention to the serious complications of phlegmonous gastritis following resection of peptic ulcer and reports cases.

H. Kapp,⁹⁵ a Swiss bacteriologist, investigated the action of silver nitrate, vaticin, enterovioform, and other drugs on the effect of the various bacteria occurring in gastritis. His observations regarding the efficacy of the drugs studied are extremely difficult to evaluate, since his diagnosis was made by bacteriologic study of the fasting gastric specimens.

Moutier,^{96, 97} in a series of gastroscopically studied cases, reports the fre-

quency of pustulous gastritis, and their clinical manifestations by chronic vomiting, etc.

Till⁹⁸ found that of 47 patients gastroscopied for dyspepsia of various kinds, and in whom x-rays revealed no definite gastric lesions, 25 were normal in gastric appearance, 10 had a superficial catarrhal gastritis, 8 a hypertrophic gastritis and 4 an atrophic gastritis. These observations made in England corroborate the larger series made in 1936 by the authors. He voices the same opinion of the REVIEWERS in stating that every patient with dyspepsia should be gastroscopied when other routine investigations are inconclusive. Borland⁹⁹ concurs with Schindler and the authors that hypertrophic gastritis is a "grave disease," and finds that in his experience in the southern section of the United States, "advanced gastritis is one of the most serious ailments of the gastrointestinal tract," since the patients are nearly always unresponsive to therapy.

Treatment—The present status of treatment of chronic gastritis has been reviewed and presented by the authors.¹⁰⁰ Due to the lack of space, this therapy can only be referred to in the 1939 Service of the Encyclopedia—since nothing new has been contributed recently to the literature on treatment of chronic gastritis.

Attention is drawn to the fact that our present methods of therapy are objectively and sometimes subjectively inadequate in the treatment of the hypertrophic and nonanemic atrophic forms of chronic gastritis. The congestive, edematous, catarrhal, ulcerative and erosive forms of gastritis are all the most responsive to medical therapy, both from the response of symptoms to treatment and from gastroscopic observation.

DISEASE OF THE GALL-BLADDER

By J. WARREN HUNDLEY, M.D.

Introduction—Although there have been many contributions to the literature during the past 2 years on the subject of extrahepatic biliary tract disease, particularly gall-bladder disease, these additions have included nothing which has fundamentally changed previously accepted ideas on the subject. From the research standpoint, no investigative work has resulted in the development of any outstanding or novel contribution to the clinical problem of gall-bladder disease and from the clinical point of view, no particularly significant new thoughts have been forthcoming.

It shall be the primary purpose of this section to review some of the exemplary contributions to recent literature, particularly in their reference to the *diagnosis* and medical *treatment* of gall-bladder disease.

Diagnosis—Of the various steps leading to the proper diagnosis of gall-bladder disease, all authorities are agreed that of primary importance is a carefully elicited and properly evaluated clinical history. The failure to attach proper significance to the history, by overemphasizing the roentgenographic and laboratory findings, still leads to many errors in diagnosis and no doubt to not a few unnecessary cholecystectomies.

The *most* frequent cause of error in the diagnosis of lesions of the biliary tract according to W. Walters,⁷⁶ has been the failure to recognize the importance and the significance of the clinical history. Especially is this the case if roentgenologic examination fails to demonstrate the presence of disease. Attention is directed to the fact that many gallstones are not opaque to roentgen rays and fail to be visualized in cholecystograms. Therefore, the roentgenologic report regarding

the number of stones visualized and their position may not agree with the number and position of the stones that actually are present. Likewise, the roentgenologic report of a nonfunctioning gall-bladder is not always an indication of the degree of pathologic change present.

Symptoms—Symptoms which persist after operations on the biliary tract can be attributed, according to Walters, directly to 1 of 2 causes: (a) There may have been failure to recognize, both before and after operation, that the patient's symptoms were not explained by the condition of the biliary tract; (b) the presence of lesions in the biliary tract other than those in the gall bladder may not have been recognized; such lesions are stones in the common or cystic ducts, cholangitis, pancreatitis, carcinoma of the bile ducts, of the ampulla or of the pancreas, and abnormal functioning of the sphincter of Oddi.

It must be remembered that other lesions may produce symptoms which mimic those of disease of the biliary tract, and the presence of these lesions must be excluded whenever possible in examination of the patient prior to operation and by exploration of the suspected structures at the time of operation on the biliary tract. Among these lesions are perforating ulcers of the posterior duodenal wall, calcareous disease of the urinary tract and hydronephrosis. To this list can be added the less frequently occurring referred pain of angina pectoris, gastric crisis of tabes and the pseudocholecystitis of neurasthenic women. Particular attention is directed to the large number of cases in which unsuspected stones are present in the common bile duct and in which jaundice never has been present, stones being found only by exploration

of the interior of the enlarged duct. In the absence of stones of the common duct, other causes of pain are pancreatitis and spasm of the sphincter of Oddi and of the duodenum.

Aside from a satisfactory history and physical examination, *cholecystography* and *duodenal drainage* remain the most valuable aids in the establishment of a diagnosis of gall-bladder pathology. The intensified (double-oral) method of cholecystography introduced by Stewart continues to prove a worthwhile innovation in the technic of this investigation, and the reports of roentgenologists in general favor its more widespread adoption.

In a comparison of oral cholecystographic findings and proved evidences of gall-bladder disease in 2669 examinations, F. J. Hodges and I. Lampe⁷⁷ concluded that a normal response to the cholecystographic test of gall-bladder function may be considered as 84 per cent accurate in excluding major inflammatory disease, while complete non-visualization of the gall-bladder is associated with major inflammatory involvement of the gall-bladder wall in 80 per cent of all cases so reported. The authors emphasize that cholecystographic examination, designed to gauge gall-bladder function, serves 2 practical purposes: (a) To materially improve accuracy in the matter of recognition of existing biliary stones, and (b) to prognosticate with reasonable certainty existing inflammatory disease of the gall-bladder. Recognition of calculi is 97 per cent reliable in those cases where sufficient concentrating power is retained to permit visualization of the gall-bladder in any degree. Impaired concentrating power of the gall-bladder was associated with cholelithiasis in 87.6 per cent of the cases in the series. The extent of this coincidence, the authors point out, may well reflect the accepted indications for sur-

gery of the gall-bladder. Cholelithiasis is always attended by some deviation from normal cholecystographic findings.

T. G. Hardman⁷⁸ concludes that oral cholecystography is capable of giving a correct indication in practically 90 per cent of instances as to whether the gall-bladder is normal or pathological. The fact that 10 per cent of errors may occur, however, is good reason for urging that the Graham-Cole test should not be used to supplant the usual clinical methods of examination, but should take its place as part of the ordinary routine investigation as a valuable aid in the diagnosis of cholecystic disease. Reference is made to the statistics of the Mayo Clinic emphasized by Kirklin in 1935, which gave confirmation of the x-ray diagnosis, whether positive or negative, in 95 per cent of cases. Hardman calls attention to the reports of Lysholm, of Stockholm, who maintains that in his clinic the average error is 1 in 100.

The value of cholecystography in the diagnosis of early cholecystitis remains a controversial point. McNee,⁷⁹ in advocating the more frequent adoption in England of biliary drainage findings as a diagnostic procedure, expresses the opinion that he is very cautious in accepting a diagnosis of *early* gall-bladder disease on x-ray evidence. In his emphasis on the value of duodenal drainage, McNee states, "I would go so far as to say that in early cholecystitis, it is at present the only diagnostic method on which we can positively rely and it is far too little used in Britain. Perhaps as in many tests of this kind, too much value was at first claimed for the method, but, of its diagnostic value in experienced hands, I have no doubt at all."

Biliary drainage, in the hands of experienced bile microscopists, continues to prove an invaluable diagnostic aid in the recognition of gall-bladder disease, and,

with the training of more clinicians in the interpretation of bile microscopy, is becoming more generally employed as a routine diagnostic procedure. In the hands of many workers, the value of biliary drainage compares favorably with that of cholecystography in the diagnosis of biliary tract pathology, particularly cholelithiasis.

W. T. Doran, J. W. Forster and L. C. B. Spier⁸⁰ at Bellevue Hospital, New York, compared their analysis of biliary drainage findings in 64 operated cases with the findings by cholecystography in 60 of the cases. Preoperative biliary drainages were done in 64 operated cases. Cholesterol crystals or calcium bilirubinate pigment or both crystals and pigment were found in the bile in 27 cases (43.5 per cent). At operation stones were present in 22 of the 27 (81 per cent). Of these 27 cases, calcium bilirubinate pigment without cholesterol crystals was present in 9 of the 10 cases (90 per cent). Cholesterol crystals were present in 11. In 10 of these, stones were present at operation (91 per cent). Both cholesterol crystals and calcium bilirubinate pigment were present in 6 cases. Stones were found at operation, however, in only 3 cases (50 per cent). Of the 48 cases having calculi at operation, 21 had crystals, pigment or both in the preoperative bile (43.7 per cent), 19 showed neither of these elements nor a concentrated gall-bladder fraction of bile. Pathological drainage findings, that is, the presence of crystals or pigment in the absence of concentrated bile, were found in 40 of the 48 stone cases (83.3 per cent). The remaining 8 patients with none (16.6 per cent) had a normal biliary drainage.

An analysis of the cholecystographic findings in 60 of the operated cases of the series revealed that while only 30 per cent of the gall-stone cases showed

stones by cholecystogram, over 93 per cent showed a pathological cholecystogram, *viz.*, calculi, no visualization, faint visualization or normal visualization with delayed emptying. Thus, in patients with cholelithiasis, cholecystography was superior in revealing pathology; 93 per cent as compared with 83.6 per cent for biliary drainage. Actual calculi were demonstrated in cholecystograms in 30 per cent of cases, while the presence of calculi was suggested by drainage findings in 43.7 per cent. When findings by biliary drainage and by cholecystography are both considered, pathology was indicated in 95.9 per cent.

In a similar study by L. J. Rigney, W. L. Mortensen and T. G. Miller,⁸¹ based on 137 operatively proved cases of gall-bladder disease, 89 per cent of their stone cases showed gall-bladder disease by roentgenography and 90 per cent by biliary drainage; of the noncalculous cases, 51 per cent by cholecystography and 59 per cent by biliary drainage. The criteria for the preoperative diagnosis of gall-bladder disease were impaired function or evidence of stone, some cases showing both abnormalities, some only one.

Treatment—A survey of the contributions to medical literature during the past few years regarding the surgical and medical treatment of gall-bladder disease seems to justify the following definite conclusions:

1. The trend is toward the more conservative management of gall-bladder disease, particularly of chronic cholecystitis without stones, the degree and likelihood of symptomatic relief by cholecystectomy being apparently more dependent on the presence of stones or a history of colic than on the pathologic condition of the gall-bladder.

2. Most surgical authorities agree that in the management of cases of acute cholecystitis, no arbitrarily set time is feasible for surgical intervention in all instances, careful individualization being necessary and exemplifying sound

surgical judgment. So important a decision cannot be based on generalizations and so complicated a disease cannot be reduced to such simple terms as "hours after onset" or "delayed," "early" or "immediate" operative intervention. Most likely the mortality rate will be higher in the hands of the majority of surgeons if "immediate" operation in all cases is advised.

3 Adequate medical management is a problem of paramount importance, but as yet no universally accepted plan of medical treatment has been forthcoming.

A critical survey of the medical and surgical management of gall-bladder disease, in the opinion of H. E. Mock, C. F. G. Brown and R. E. Dolkart,⁸² leads to the inevitable conclusion that present-day therapy is inadequate. From the surgeon's point of view, the consensus is that if there is any evidence of pathological changes in the gall-bladder, the structure should be immediately removed. From the internist's point of view, the use of the low fat, low cholesterol diet, in conjunction with catharsis, comprises the average conception of the medical management of gall-bladder disease and has remained unchanged as the treatment of choice for many years. The authors do not concur with either conception. They emphasize that the available data indicate quite definitely that approximately one-third of all patients subjected to biliary tract surgery show little or no improvement after operation, signifying a definite need for a more careful selection of cases for surgery. Apparently the best subjective results are obtained in patients submitted to surgical intervention who give histories of repeated colic, common duct stone, or chronic pancreatitis, whereas the poorest results have been obtained in patients in whom cholecystitis existed without cholelithiasis.

In the outline of their plan of medical treatment, Mock, *et al*, include the following: (a) Administration of *keto-*

cholanolic acid to stimulate the flow of hepatic bile; (b) *frequent feedings of milk and cream* to induce contraction and emptying of the gall-bladder at regular intervals, and (c) antispasmodic and sedative medication (*belladonna* and *phenobarbital*) to diminish the irritability of the gastrointestinal tract, thereby alleviating stasis. In severe cases, *bed rest* was necessary at the time this form of management was instituted.

In the absence of other indications, there are 3 types of gall-bladder disease which the authors believe will respond to physiological medical management: (a) The gall-bladder dyskinesias; (b) chronic cholecystitis without stones, and (c) chronic cholecystitis with large soft calculi, few in number, and with which the patients have no, or very infrequent, colic-like attacks. Even in this latter group it was found that a large number of patients became relatively symptom-free when treated by the methods described. Such patients, however, who do not respond to a reasonable trial period of such therapy should receive surgical treatment without further delay.

These authors conclude that they believe that the present conceptions of the medical management of gall-bladder disease using low fat, low cholesterol diets in conjunction with saline purgatives have no sound physiological basis. On the basis of their studies of 120 patients with chronic disease of the gall-bladder, they found that the use of the 3 principles of therapy previously mentioned effectively relieved the symptoms and reduced the incidence of colic in the majority of cases treated. It is emphasized that there should be a definite revision of ideas as to what constitutes indications for surgery in patients with chronic gall-bladder disease.

A different opinion regarding the value of a low cholesterol diet is presented by

J. R. Twiss and J. H. Barnard,⁸³ based on a series of 110 medical and surgical patients with disease of the gall bladder and associated hypercholesteremia, treated with a low cholesterol diet. A control series of 35 patients did not receive such a diet. By repeated chemical analyses, the blood cholesterol in cases of hypercholesteremia was reduced following the *low cholesterol intake* and symptomatic relief resulted in most of such cases.

These investigators believe that the diet is indicated also after cholecystectomy to preclude hypercholesteremia and recurrent symptoms.

As a program for the medical management of chronic gall-bladder disease, A. I. Levin and M. Shushan⁸⁴ list the following measures as being fundamentally helpful in restoring normal gall-bladder and biliary tract function:

1 *Proper hygienic régime; regularity in meals; rest after meals, adequate sleep, etc.*

2 *Outdoor exercise; deep breathing.*

3 *Avoidance of constipation.*

4 *Frequent small meals* for gall-bladder drainage

5 *Bland, nonirritating diet, low in fat* to avoid excessive biliary tract stimulation and tendency to hypercholesteremia. *High fat diets* for stimulating gall-bladder emptying when these are not contraindicated by inflammatory conditions or hypercholesteremia. *Caloric adjustments* for obesity and malnutrition

6 *Removal of foci of infection.*

7 Selected medication, *saline cathartics, bile salts, cholagogues, sedatives, antispasmodics.*

8 *Biliary tract drainage.*

9 Application of *heat to abdomen.*

10 *Avoidance of alcohol.*

11 *Alkaline mineral water;* liberal intake of *fluids* generally and *hot water before meals.*

DISEASES OF THE PANCREAS

By THOMAS A. JOHNSON, M.D.

Cystic Fibrosis of the Pancreas

D. H. Andersen¹⁰¹ reviewed all the reported cases of cystic fibrosis of the pancreas. That condition occurs more often in infants, and, not infrequently, is difficult to differentiate from celiac disease. Pathologically, in cystic fibrosis of the pancreas the acinar tissue of the pancreas is replaced by epithelium-lined cysts. The islands of Langerhans remain intact. The resulting lack of pancreatic enzymes in the small bowel is reflected in a variety of abnormalities. The stools contain large amounts of neutral fat which represent a depletion of caloric intake. The inability to digest a normal amount of fat results in a decreased absorption of the fat-soluble vitamins. The inadequacy of vitamin A

probably is related to a tendency for these children to die of varying types of lung pathology, *i e.*, bronchitis, bronchiectasis, pulmonary abscess and lobular pneumonia. Deficient absorption of vitamin D or calcium or both gives rise to varying degrees of osteoporosis. Fatty degeneration of the liver has been reported at autopsy. Referring to the difficulty in differentiating cystic fibrosis of the pancreas from celiac disease, Anderson states that the clinical picture of celiac disease may be presented by patients with pancreatic insufficiency who survive the first year of life. The presence of normal pancreatic enzymes in the duodenal contents would favor the diagnosis of celiac disease as against pancreatic insufficiency secondary to cystic

fibrosis of that organ. Andrews further states that stool criteria of differentiation between those 2 conditions is unreliable

J. Thomas and F. W. Schlutz¹⁰² believe that the preponderance of fatty acids in the stools of patients with celiac disease, and in whom pancreatic function may be considered normal, is of sufficient consequence to differentiate celiac disease from the pancreatic steatorrhea secondary to congenital pancreatic fibrosis

In view of the well-known experimental evidence of fairly adequate fatty digestion in animals who have been subjected to pancreatic duct ligation, this REVIEWER is inclined to agree with Andrews concerning the unreliability of stool examinations as evidence of pancreatic insufficiency. However, the REVIEWER feels that the utmost caution should be observed in interpreting the clinical importance of decreases in pancreatic function as measured by decreases in the enzymes in duodenal juice. The present methods of determining the enzymes in duodenal juice are adequate if normal values are obtained but decreased values may be the result of so many variables other than pancreatic dysfunction that one hesitates to accept them without that qualification

Lipocaic

In 1936 L. R. Dragsted¹⁰³ and his coworkers reported studies on a new fat-free alcoholic pancreatic extract, lipocaic, the administration of which prevented the deposition of fat in the livers of depancreatized dogs maintained on insulin. In effect, they called attention to a new fat-metabolizing, lipolytic hormone. Numerous investigators^{104, 105} previously had noted that the marked hepatic enlargement which developed in pancreatectomized dogs could be pre-

vented by the addition of raw pancreas to their diets. Pathologic studies of the enlarged livers showed that the change was the result of fatty infiltration. There is a difference of opinion concerning the nature of the essential factor in the raw pancreas which prevents fatty infiltration of the liver. Apparently the factor is absent in the pancreatic juice. Certain other substances have been shown to exert similar lipolytic effects on the liver in experimental animals, namely, choline,¹⁰⁶ casein,^{107, 108} lecithin,¹⁰⁹ and betaine.¹⁰⁷

C. H. Best and J. H. Ridout¹¹⁰ believe that there is insufficient evidence to warrant the acceptance of lipocaic as a new entity. Moreover, the same writers aver that lipocaic exerts only the effect which could be predicated by its choline or protein content. A similar view has been expressed by E. M. MacKay and R. H. Barnes¹¹¹ who, in addition, report that the fatty liver secondary to administration of anterior pituitary extract is not influenced by either choline or lipocaic. F. F. Boyce and F. M. McPetridge¹¹² note that fatty metamorphosis of the liver does not occur after excluding pancreatic secretions from the duodenum by duct ligation as long as the pancreas itself remains intact.

Although investigators disagree concerning the nature of lipocaic and its mode of action, several interesting clinical applications have been reported. H. G. Grayzel and L. S. Radwin¹¹³ treated 3 young diabetic patients in whom persistent hepatomegaly was observed. With ordinary diabetic management, including insulin, there was no reduction in the size of the livers. Administration of Dragstedt's lipocaic resulted in a prompt recession of the hepatomegaly so that the livers returned to normal size. A lowering of the blood lipids likewise was accompanied by the return to nor-

mal. The authors found that it was necessary to administer lipocaic continuously to prevent recurrence of the hepatomegaly. It would be of interest to compare the effect of raw pancreas or choline in similar cases, although in 1934 E. S. Judd, E. J. Kepler and E. H. Rynearson¹¹⁴ observed no beneficial effects from the administration of choline and betaine to 2 patients with fatty livers in association with hypoglycemia.

A. M. Snell and M. W. Comfort¹¹⁵ noted a rapid decrease in the size of the liver in a case in which they used lipocaic. Unfortunately the case of Snell and Comfort lacked biopsy proof of fatty metamorphosis of the liver.

D. H. Rosenberg¹¹⁶ reported a proved instance of recovery from fatty metamorphosis of the liver in association with diabetes mellitus. During the course of a laparotomy for removal of a pathologic right ovary an enlarged fatty liver was found and a section taken for bi-

opsy which, on microscopic examination, was thought to be fatty metamorphosis of the liver. Subsequently the patient took 5 Gm. of Dragstedt's lipocaic by mouth daily for 12 weeks during which the liver receded from 10 cm. below the midclavicular line to 1.5 cm. below the midclavicular line. Then the patient was operated upon for severe biliary colic and the gall bladder removed. At the second operation a striking change was noted in the liver. Whereas it had been yellowish and mottled previously, it was now uniformly reddish brown in color, and normal in size and consistency. A second biopsy specimen on histologic examination revealed an almost normal liver structure. The patient showed a corresponding improvement in her liver function studies. The above case represents the first recorded instance in the human in which there was a definite return of a fatty liver to normal under the influence of lipocaic.

VITAMINS

By JOHN H. WILLARD, M.D.

Vitamin A

A review of the present information concerning vitamin A has been published by O. A. Bessey and S. B. Wollbach¹¹⁷

Physiology—Studies have indicated that no vertebrate can synthesize carotenoids, or the provitamins, but that all higher animals can convert certain carotenoids to vitamin A. The occurrence of these carotenoids is closely related to chlorophyll, so that the quantity of chlorophyll is an index to the carotene content of green plants. Human intake of the provitamin depends largely on consumption of green and yellow vegetables. Eggs, milk and butter furnish vitamin A as well as some carotene.

Animals have been found to have a large storage capacity for vitamin A. About 95 per cent of the total body content of this vitamin is present in the liver, and it is believed that excess feeding may store sufficient vitamin to last for several years (if the results of rat experiments can be applied to humans). The vitamin A content of human liver from well-nourished subjects is from 200 to 400 international units per gram or from 10 to 20 mg. per 100 Gm. Hepatic reserves may be lowered by chronic disease or infection either as a result of decreased assimilation or increased demands. Liver disease is a theoretical source of deficient reserve, but adequate

proof is as yet lacking, according to Bessey and Wolbach. Experiments seem to indicate that storage occurs in the Kupfer cells since hepatic toxins like phosphorus do not reduce vitamin A content while blockage of the reticulo-endothelial system lessens the hepatic storage. Since in jaundiced dogs the use of carotene is inhibited, a certain amount of fat absorption from the intestine seems essential. Chronic diarrhea, biliary obstruction, pancreatic dysfunction, celiac disease and other fat disturbances may result in vitamin A deficiency.

Pathology—One of the earliest functional changes in vitamin A deficiency is decreased ability for dark adaptation, night blindness. Clinical investigations of this function by use of photometric tests (Jeans, *et al.*, Jeghers, Palmer and Blumberg, Park, Corlette, *et al.*, and Barborka) have shown an apparent frequency of vitamin A deficiency. B. L. Isaacs, F. T. Jung and A. C. Ivy¹¹⁸ have questioned the accuracy of these observations. Tests were done on 143 medical students and the results subjected to statistical analysis. It was found that while the intake of vitamin A varied from 1650 to 9725 I. U. per day no correlation could be detected between dietary intake and biophotometric readings. Neither was there any correlation between vitamin A intake and clinical signs and symptoms of deficiency. It was concluded by these workers that "the criteria generally chosen for the recognition of vitamin A deficiency by means of the biophotometer are not the most reliable criteria. Far more study is essential before the biophotometer or any similar instrument can be used *per se* for the detection of vitamin A deficiency in the human being."

The pathologic changes in vitamin A deficiency have been described in detail by S. B. Wolbach.¹¹⁹

Requirements—L. E. Booher¹²⁰ reviewed various studies on daily requirements of vitamin A based on photometric determinations and diet calculations and concluded that from the evidence at hand the prevention of night blindness required a minimum of from 25 to 30 units per kg. of body weight daily, or approximately 1400 to 2000 units for an adult of 70 kg. An adequate safe figure would be about 3000 units. Children's requirements are probably higher, 6000 to 8000 units. Pregnant women should have an allowance of about 5000 units.

A study of dietary intake of vitamin A in various localities has shown a striking variation in different groups, largely related to economic status. Many members of families in the lower income groups are probably on the border line of recognizable vitamin A deficiency, according to Booher. The League of Nations Health Organization recommended an allowance of 500 cc. of whole milk, 1 egg, 25 Gm. of butter and a serving of a green leafy vegetable daily as being adequate. For children between 2 and 14 years the allowance should be 1 quart of milk, 1 egg, servings of green leafy vegetables and butter in proportion to size, and 3 Gm. of cod-liver oil. During pregnancy this commission advises 1 quart of milk, 1 egg, 1 ounce of cheese, an average serving of a green leafy vegetable and 1 teaspoonful of cod-liver oil daily.

Vitamin B Complex

Recent developments, including isolation and synthesis of some of the components of the B complex and the biologic effects of these fractions, have clarified to some extent the confusion regarding vitamin B.¹²¹

Most discussers divide the field into ·

1. *Vitamin B₁*, the antiberiberi vitamin that prevents beriberi in man and polyneuritis in animals (and probably man)

2 *Riboflavin*, a compound necessary for growth in chicks and rats and also the prevention of cataracts in rats.

3. *P P factor*, a nutritional factor effective in the prevention and cure of human pellagra—now believed to be *nicotinic acid*, probably identical to the *filtrate factor*, a factor for the prevention of a nutritional dermatosis in chicks and which is effectual in treating black tongue in dogs.

4 *Vitamin B₃*, a factor necessary for rapid gains in weight and normal nutrition of pigeons

5 *Vitamin B₄*, a factor for the prevention of specific paralysis in rats and chicks

6 *Vitamin B₅*, a factor necessary for maintenance of weight in pigeons

7 *Vitamin B₆*, or H, a factor for the prevention of a nutritional dermatosis in rats

8 *Factor H'*, a factor necessary for growth of rats

From a practical clinical standpoint only 2 members of this complex have been definitely linked to human deficiency disease, namely *B₁* and the P. P. factor which is undoubtedly *nicotinic acid*

Vitamin B₁—This fraction has been isolated and synthesized and the name thiamin (chloride, bromide, sulfate, etc.) has been accepted by the Council on Pharmacy and Chemistry of the A. M. A. It is necessary to the life and well-being of man and possesses antineuritic and antiberiberi properties. Its activity in the body has to do with oxidation of carbohydrates, pyruvic acid and probably lactic acid.

Requirements—C. R. Cowgill¹²² has reviewed in detail the experimental work bearing on the physiology of vitamin B₁ and on human requirements.¹²³ This author has developed a formula for determining requirements based on body weight and caloric intake. A simple statement of average requirement is 10 I. U. per 100 calories of food intake (1 mg. of thiamin chloride is equal to 300 to 500 I. U. depending on method of assay used). This estimation agrees closely with other published figures. The Coun-

cil on Pharmacy and Chemistry of the A. M. A. states that the daily requirement for vitamin B₁ appears to be not less than 50 I. U. for the infant and 200 I. U. for the adult (N. N. R. 1938, 471-2). These figures are definitely minimal and do not represent the needs under various conditions. Some of these conditions which increase the demand, according to Cowgill, are: (a) *Increased metabolism* as a result of marked physical activity, hyperthyroidism, febrile states. Under such demands Cowgill suggests an estimate of daily caloric exchange and that not less than 15 to 20 I. U. of the vitamin be provided for each 100 calories. With evidence of chronic deficiency it is suggested that the daily administration of 5 to 10 mg. of thiamin for a week to build up reserves would be of use, with a continued dose of 15 I. U. per 100 calories. (b) *Loss through excretory channels*. Since tests have shown vitamin B₁ in the urine, any condition resulting in diuresis may increase excretion. Under these conditions Cowgill recommends an increase in intake to 20 I. U. per 100 calories. It is also suggested that in any condition where large volumes of fluid are administered, thiamin should be added. Diarrhea has also been found to increase requirements.¹²⁴ With moderate diarrheas in dogs it was found that 50 to 70 per cent of the vitamin was lost. It is suggested that with diarrhea a dosage of at least 20 I. U. per 100 calories be given orally, or 15 I. U. per 100 calories be given parenterally.

As yet no simple laboratory tests of vitamin B₁ levels in blood or urine have been devised. However, L. J. Harris and P. C. Leong,¹²⁵ testing urine with the rat bradycardia test described by these authors in 1936, have reported their results in a variety of conditions. Resting levels and response to test doses

of 300 to 950 I U were recorded and the following standards suggested:

Normal.

Resting Level 10 to 20 I U.

After test doses of 350 I U. Response to 30 I U.

Subnormal.

Resting Level Less than 10 I U

After test dose Response to 15 I U

Therapeutic Indications—According to M. B. Strauss¹²⁶ vitamin B₁ deficiency in man involves especially the nervous and circulatory systems. The neural symptoms usually are noted first in the extremities and consist of heaviness of the legs and tenderness of the calf muscles. Increasing fatigue on exercise appears and later foot drop may occur. The upper extremities are involved later. Cranial nerves are seldom involved but memory defects are common. These effects differ from the polyneuritis of lead poisoning in which only motor nerves are affected, pain being absent. Infectious polyneuritis usually involves the shoulder girdle or thighs and cranial nerves, the involvement is proximal with peripheral spread. The cardiovascular signs of beriberi are dyspnea, palpitation, tachycardia and edema. Cardiac enlargement to both right and left occurs. A low blood pressure but with a bounding pulse is common. Other manifestations are anorexia, nausea, glossitis, achlorhydria, anemia and diarrhea. There is doubt that these evidences of deficiency are solely due to B₁ deficiency.

Dosage Vitamin B₁ may be given in pure form or in substances rich in this vitamin. In a definite case of beriberi Strauss recommends intramuscular or intravenous injection of from 20 to 50 mg. of thiamin daily. After a fortnight similar doses orally may be employed or 10 mg. daily parenterally. Brewer's yeast, plain or autolyzed, is a good source

of the B complex. Thirty grams of a potent source of yeast given 3 times daily is usually a sufficient dose for moderately ill patients if there is no evidence of impairment of intestinal absorption. Strauss stresses the frequent association of deficiencies of other B fractions as well as vitamins A, C and minerals in beriberi and suggests the inclusion of adequate amounts of these. The duration of treatment will of course vary markedly. In acute nerve lesions recovery may appear in a week. With actual degeneration recovery is slow and may be calculated at about 1 mm. per day.

Nicotinic Acid—Since the report of Flyvbjerg, Strong, Madden and Woolley¹²⁷ in 1937 on the curative effects of nicotinic acid in "black tongue" of dogs, numerous reports have appeared concerning the curative value of this material in pellagra. According to reviews by Spies and his associates,^{128, 129} nicotinic acid, nicotinic acid amide, sodium nicotinate and coramine are effective in treating pellagra. Dimicotinic acid isolated from liver extract has also proved effective.

Indications¹³⁰ The clinical diagnosis of pellagra is based on the presence of the typical dermatitis, stomatitis, gastrointestinal and nervous symptoms. Early or prodromal symptoms may include loss of weight and strength, insomnia, lassitude, vertigo, headache, anorexia, and diarrhea. Later stomatitis appears. Skin lesions are usually present and are characterized by their sharp margins, bilateral symmetry, manner of evolution, pigmentation and keratosis. They begin as dark red areas which become confluent and gradually darker in color. Scaldiness with thickening and sometimes bullae and vesicles appear, and atrophy of the skin follows. The commonest sites are the dorsal surfaces of the hands, lower forearms and neck.

Irritation of the labia and buttocks is common. Mental symptoms are very common and consist of depression, melancholia, lethargy and stupor. Confused states and hallucinations may appear. Paresthesias, tremors, muscular cramps and paralysis of the lower extremities also occur. Recent evidence suggests that these peripheral nerve changes may depend on an associated vitamin B₁ deficiency rather than on pellagra *per se*.

The symptoms and signs in the 73 cases reported by Spies,¹²⁹ *et al.*, were as follows.

	Cases
Loss of weight, strength and appetite	73
Mucous membrane lesions	73
Characteristic skin lesions	56
Mental symptoms	51
Diarrhea	40
Urethritis	27
Severe vomiting	24
Peripheral neuritis	23
Vaginitis	23
Proctitis	21
Constipation	10

Dosage—All of the symptoms of pellagra seem to respond to nicotinic acid therapy. Spies and his coworkers administered from 50 mg. to 1 Gm. orally per day in doses of from 20 to 500 mg. They suggest 50 to 100 mg. 5 or 6 times daily, the average daily amount being 500 mg. In some cases, parenteral administration may be advisable in doses of 10 to 20 mg. intravenously. Reactions occurred in some patients with large doses and consisted of flushing, burning and itching of the skin. Studies by these writers on 100 adults without pellagra showed these reactions to occur in a few individuals with a 50 mg. dose in water on an empty stomach, in 50 per cent of those given 100 mg., and in all of those given 500 mg. doses.

Results—All writers to date have reported prompt relief of symptoms

Spies, *et al.* (*ibid.*), reported blanching of the skin lesions, improved gastrointestinal function, remission of mental symptoms and a decrease in porphyrinuria within 72 hours after large doses. A feeling of well-being frequently appeared in 24 hours, and a similar rapid improvement occurred in the mucous membranes of the mouth, throat, rectum, urethra and vagina. Peripheral neuritis was not relieved until vitamin B₁ was added. It is of interest that severe Vincent's gingivitis responded to nicotinic acid within 24 to 48 hours.

Vitamin C

Since synthesis of vitamin C in 1933, a great volume of investigative and clinical work has been published. While there is much remaining to be known, there is fairly definite information regarding human requirements, effects of deficiency and food sources. Definite deficiency (scurbic) states are indicated by spongy bleeding gums, hemorrhagic tendencies, sore and swollen joints, increased capillary fragility and edema. The pathologic processes are the result of failure of production of the intercellular cement substances in endothelial tissues. Hemorrhagic phenomena are usually the outstanding clinical features. Relationships have been suggested between vitamin C and dental conditions, endocrine disturbances, gastrointestinal diseases, immunity, response to infection, and wound healing. Recent work has questioned the importance of vitamin C deficiency in the etiology of rheumatic fever formerly suggested by Rhinehart. A. D. Kaiser¹³¹ studied the ascorbic acid content of the plasma in rheumatic children and adults. While reduced levels were present in some, and urinary output has been found low by other investigators, this writer feels that his studies failed to support the theory that vitamin C defi-

ciency is of etiologic importance in rheumatic fever and other rheumatoid states.

Requirements—Human requirements have been set at about 600 to 1200 I. U. daily for normal adults.¹³² Infections and pregnancy probably increase body needs. One milligram of cevitamic acid is equal to 20 I. U., so that a 30 to 60 mg. daily intake is regarded as adequate. The best sources include orange, lemon and grapefruit juice, tomato and raw cabbage juice, and strawberries. Canned tomato and citrus fruit juices are also good sources. The relative content of various foods has been listed by O. A. Bessey.¹³³

Tests of Deficiency—*Urinary excretion* with or without test doses of ascorbic acid has received much attention. The quantity of ascorbic acid required to induce saturation and subsequent excretion in the urine appears to be a measure of the state of vitamin C nutrition of the patient. According to Abt and Farmer, vitamin C appears to be selectively absorbed by the intestinal tract, especially by the small bowel. In achlorhydria, blood levels are usually lower than normal, possibly due to increased destruction by intestinal bacteria. The authors point out that, until more information is available, it must be assumed that there are individual variations in absorption and that under certain conditions absorption may be definitely abnormal. While blood levels and urinary excretion may be indicative of the state of body saturation, it is necessary to consider intestinal absorption of test doses in using urinary excretion as a measure of deficiency. It is also believed that there is considerable variation in the renal threshold for cevitamic acid. C. C. Ungley¹³⁴ quotes Elmby, *et al.*, as finding that in chronic intestinal lesions, oxidation of ascorbic acid to dehydroascorbic acid may be interfered with. Under

these conditions, lemon juice is a more effective source than synthetic vitamin C. Bessey states that: "Provided manipulations are carried out properly and interpretation of too fine a character are not attempted, the method is of real value." Ungley (*loc. cit.*) advises the use of intravenous test doses to eliminate the intestinal absorption factor. Ascorbic acid begins to appear in the urine when blood saturation reaches about 1 mg. per cent, although a low renal threshold may occur. (A case of renal scurvy was reported by C. A. Mawson¹³⁵) Normally a 600-mg. oral test dose is followed in 3 hours by some excretion in the urine; this is not true in deficiency states. I. S. Wright and his coworkers¹³⁶ suggest a test intravenous dose of 1000 mg. Normally at least 400 mg. are excreted in the urine during the following 5 hours, according to these workers. A variation may be found in patients with renal disease and nitrogen retention, in which case parallel blood and urinary studies are of value.

Blood cevitamic acid determination is probably the simplest procedure giving a maximum amount of information, according to Wright and Abt and Farmer. Normal blood levels are between 0.7 and 1.3 mg. per cent. Values below 0.7 mg. per cent are subnormal or at least suboptimal. Scurvy may occur with values below 0.4 mg. per cent.

Spinal fluid levels have been studied by H. Wortis, J. Liebmman and E. Wortis¹³⁷ in association with blood levels and urinary excretion. These writers concluded that a blood level above 0.7 mg. per cent was almost invariably associated with a normal spinal fluid content and a normal urinary excretion test. With subnormal blood levels (below 0.4) there was almost invariably a subnormal spinal fluid content and a low urinary excretion test.

Capillary fragility has been suggested as an index of vitamin C nutrition. Abt and Farmer state that "a clear relationship between capillary resistance of the skin and dietary intake of vitamin C has not been definitely established." However, Wright feels that properly conducted tests may be of value. He advises placing the blood pressure cuff on the upper arm for 15 minutes with a pressure midway between systolic and diastolic readings. Two circles, $2\frac{1}{2}$ cm. in diameter, are drawn on the inner smooth surface of the forearm at least 4 cm. below the elbow crease. Five minutes after release of the pressure the number of petechiae can be counted with the naked eye. The normal response for adults is 10 spots or less per circle. Ten to 20 spots are regarded as borderline and more than 20 spots indicates definite pathology. While this writer does not feel that the test is infallible, it is a simple suggestive finding.

Other conditions may produce increased fragility such as poisoning (nearsphenamine, carbon monoxide), toxins (scarlet fever, subacute bacterial endocarditis, diphtheria), and metabolic products (anemia, acetonemia, menstruation). Confirmation by chemical tests of vitamin C saturation should be done in any questionable case. J. Liebmann, H. Wortis and E. Wortis¹³⁸ tested 88 patients for capillary fragility by means of the cuff method of Wright and the suction cup method of Dalldorf. They found that a normal blood value was associated with normal capillary fragility in 74 per cent by Wright's method, while subnormal blood levels were associated with normal fragility tests in 30 per cent. No correlation of blood levels and fragility by the Dalldorf test was found, petechiae appearing in 63 per cent of normal blood cases. They concluded that "abnormal fragility tests should be considered as

being due to vitamin C deficiency only if: (a) The vitamin C in the body fluids is low; and (b) if the fragility returns consistently to normal following adequate vitamin C therapy."

An intradermal test was reported by Porter and Wilkinson.¹³⁹ A dye, dichlorophenolindophenol, was injected into the skin and the length of time necessary for disappearance of the color was recorded. Normals took 5 to 10 minutes, while deficient patients took more than 10 minutes. Wright states that in his experience this test is unsatisfactory because of the great range of error.

Dosage—According to Wright, the curative dose of cevitamic acid is usually between 30 and 50 mg. per day orally, although in extreme cases 1000 mg. daily may fail to produce a favorable response. Overdosage does not appear to be harmful. This writer has given as much as 10,000 mg. intravenously in a single dose and has administered 1000 mg. daily for months without untoward effects. For clinical purposes it is suggested that 30 to 1000 mg. orally or intravenously and up to 100 mg. intramuscularly each day may be given without danger.

Vitamin P—The work of Szent-Gyorgyi in 1936 indicated the presence in citrus fruit juices of a substance which assisted the action of ascorbic acid in certain hemorrhagic states. While this substance, vitamin P or "Citrin," alone was not effective in treatment of scorbutic states, it was found to increase the effectiveness of synthetic vitamin C. T. Jersild¹⁴⁰ reported a case of Shonlein-Henock Purpura in which the capillary fragility test was not improved by ascorbic acid intravenously but which did improve on the addition of citrin in 50 mg. doses intravenously per day. Capillary fragility increased on stopping citrin and again was reduced by its readministration.

Vitamin D

This vitamin is concerned primarily with calcium metabolism and is of particular interest in connection with rickets, osteomalacia, renal rickets, idiopathic steatorrhea, celiac disease and possibly in arthritis. C. E. Bills¹⁴¹ reviewed the chemistry of vitamin D and reported 10 different sterols which may exhibit the properties of this vitamin. Five of these are well understood chemically and 5 are known only by fragmentary chemical and physiologic differences. "The 2 that are of prime importance are the activation products of ergosterol and 7-dehydro-cholesterol respectively." Irradiated ergosterol is also known as calciferol or vitamin D₂, 7-dehydro-cholesterol is the form primarily found in animal products such as fish oil and eggs. It is of interest that the 2 products have the same anti-rachitic effects in rats while the latter is much more effective in chickens. The latter product has been called vitamin D₃.

Sources and Requirements—F. M. Nelson¹⁴² reported on the sources of vitamin D and states that biologic assay is still necessary for proper standardization. The potency is the same in both U. S. P. and international units. "Most foods appear to be devoid of demonstrable quantities of vitamin D. Fish which contain much body fat, such as salmon, sardines and herring are the richest natural source, eggs are next in importance, and milk fat and meal products contain some vitamin D. Vitamin D milk is now being used extensively as a dependable source of vitamin D." Pharmaceutical preparations must be relied upon for additional supplies.

According to P. C. Jeans and G. Stearns,¹⁴³ the requirements are variable and depend largely on the ability to utilize calcium and phosphorus and the adequate supply of these elements. A full

term artificially fed baby probably requires between 300 and 400 units per day, prematurely born babies may require twice as much. Between infancy and adolescence an allowance of at least 750 cc of milk together with from 300 to 400 units of vitamin D is adequate. During adolescence the need is probably about 300 units per day, while the optimal amount for adults has not been definitely determined. During lactation and pregnancy there is probably an increased demand and a daily dosage of 800 or more units is suggested together with an abundant intake of calcium and phosphorus.

Vitamin E

As yet the importance of this vitamin in the human has not been definitely proved. According to R. M. Wilder and D. L. Wilbur,¹²¹ the value of wheat germ oil in habitual abortion requires more clinical evidence.

Vitamin F

While various reports have appeared regarding the value of certain unsaturated fatty acids (known as vitamin F) in skin abnormalities, there is a lack of any well-established facts to justify their use, according to Wilder and Wilbur (*ibid*).

Vitamin K

A fat soluble factor has been described by A. M. Snell and H. R. Butt¹⁴⁴ and K. M. Brinkhous, H. P. Smith and E. D. Warner,¹⁴⁵ which is related to the hemorrhagic tendency in jaundice. Previous investigations have shown that this hemorrhagic state could not be attributed to a deficiency in calcium, fibrinogen, blood platelets or thromboplastin, and it seems quite certain that any regurgitated elements of bile in the blood stream are not a causative factor, according to Snell. The first evidence that a substance necessary for coagulation was lacking was

produced by Quick and his associates (1935). These investigators showed that in jaundice there is a diminished quantity of prothrombin in the blood, and that such deficiency was responsible for the disturbance in coagulation. Such a deficiency was found in chicks fed on diets lacking in certain fat soluble substances, in experimental animals with biliary fistulas, in dogs with damaged livers and in cattle fed on toxic sweet clover hay. In 1935 Dam reported a fat soluble substance which he called vitamin K (Koagulations vitamin). This substance has been obtained from a large number of sources including pig liver fat, dog liver, beef liver, alfalfa, kale, carrot tops, tomatoes, soy bean oil, egg yolk, fish meal, rice bran, and various bacterial cultures.

Snell and his associates believe that 2 factors are necessary to maintain normal prothrombin concentration. The presence of bile in the bowel and this hypothetical fat soluble vitamin. Liver function may be a third factor of importance.

Using Quick's method of determining prothrombin time, these authors have not seen an abnormal tendency to bleed in any case with a normal test, whereas free bleeding may occur with increased prothrombin times (decreased prothrombin). The danger period is usually between the first and seventh postoperative day.

Snell,¹⁴⁶ *et al.*, have reported their experience with 73 patients. Fish meal was the earlier source of vitamin K, later an extract of alfalfa was employed. No exact dosage has been possible because of varying potency. For prophylactic use in jaundiced cases in which surgery was contemplated, 2 to 6 gelatin capsules, each containing 200 mg. of alfalfa concentrate (Abbott Laboratories) and 1 to 2 Gm. of animal bile salts were given. These workers have used Desicol sodium desoxycholate, Bilron, Bilem and human

fistula bile. In cases with bleeding or a high prothrombin time, larger doses were needed, often requiring administration *via* duodenal tube. Two to 4 Gm. of bile salts dissolved in 250 to 500 cc. of warm saline solution or tap water with 1 to 2 Gm. of alfalfa concentrate were administered by the drip method. The prothrombin time was usually reduced within 6 to 12 hours. Dam and Glavind are quoted as obtaining results by intramuscular injection of vitamin K concentrates.

Results—Without use of vitamin K before surgical intervention, the writers found bleeding to occur postoperatively in 64 per cent of 14 cases of jaundice. In 7 of these, the bleeding was later controlled by bile salts and vitamin K. Of 28 cases in which concentrates of vitamin K and bile salts were given pre- and postoperatively, bleeding occurred in only 3 (11 per cent) and was of minor importance. Of 22 cases in which prothrombin time was normal before operation and in which bile salts and vitamin K were given prophylactically, bleeding occurred in only 4 per cent.

Brinkhous, Smith and Warner (*loc cit*) gave extractions for 200 to 400 Gm. of alfalfa daily to each of 27 cases of obstructive jaundice. Six of these had shown a distinct bleeding tendency and a prothrombin level reduced below 35 per cent of normal. This reduction was improved by the extract and bleeding ceased. Some of the patients showed marked reduction in prothrombin but did not bleed.

Administration of vitamin K has not proved of value in cases of hemophilia, menorrhagia, metrorrhagia or in essential hematuria. Snell (*ibid*) reports 2 cases of hemorrhagic states, 1 due to sprue and the other to small bowel short-circuiting, which were benefited by vitamin K. This emphasizes the importance of proper

small bowel absorption in maintaining normal prothrombin, according to this author.

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HEMATOLOGY

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There has been no startling new advance in the field of hematology during 1938. The articles have been extremely numerous, however, and for the most part of interest. A decade of intense activity in the field of pernicious anemia has now drawn to a close, and hematologists are concerning themselves with other fields. That of hemolytic jaundice and of the various hemolytic syndromes is occupying a prominent place and some outstanding advances may be expected shortly. The hemorrhagic tendency in prolonged obstructive jaundice and its relationship to vitamin K deficiency has received prominence. Impaired nutrition, vitamin deficiency and anemia are the subjects of many articles. Marrow studies of one sort or another during life are now becoming almost routine

A. Blood-Forming Organs

Bonemarrow—E. E Osgood¹ continues his studies on culture of the human marrow. His apparatus is becoming

more and more simplified, and with it he has studied the effects of sulfanilamide upon streptococci, maturation of leukocytes, and the histogenesis of blood and marrow cells. Osgood concludes that sulfanilamide neutralizes the toxins liberated by the hemolytic streptococcus. His recommended nomenclature for blood and marrow cells has become rather involved, its use does not appear to be justified. Tables for the ready identification of blood cells are given. Using these tables, a technician is said to be able to identify readily a cell which "has never been heard of nor seen before." W Dameshek, H. H Henstell and E H Valentine² discuss biopsy methods and conclude that although simple puncture is easy, it frequently leads to erroneous diagnosis. The trephine biopsy, although more difficult, permits one to obtain both sections and direct marrow smears. It is important to have both a topographical view of the marrow as well as merely

a few marrow cells mixed with a relatively large quantity of blood.

Spleen—Splenic punctures are being reinvestigated. A recent article is that on the "Splenogram" by T. Tempka and M. Kubiczek.³ These authors cite previous investigations, which have been made for the most part in Italy and Spain, although recently French investigators have become interested. The technic is simple—a long, thin needle attached to a 5 to 10 cc. syringe is rapidly introduced for a distance of about 4 cm. at the point of absolute dullness in the splenic region (or below the costal margin when the spleen is readily palpable). A small amount of bloody material is obtained which is spread on slides and stained. It is recommended that the patient lie quietly for 24 hours after the procedure with an ice bag over the puncture site. Contraindications are hemorrhagic conditions or possibly infected areas in the neighborhood of or within the spleen. Normally, only lymphocytes and reticulum cells are obtained, although a certain number of nucleated reds, granulocytes, and broken-down platelets may be found. Apparently, no serious accidents have occurred. The REVIEWER has thus far hesitated to utilize this method because of its inherent dangers and because of the questionable findings which might be obtained. In cases of splenomegaly, particularly of obscure origin, the REVIEWER recommends biopsy of the marrow, because usually when the spleen is involved, there is concomitant involvement of the marrow. Nowhere is this more striking than in Gaucher's disease.

B. Hematological Methods

The Evelyn photoelectric colorimeter⁴ is rapidly displacing ordinary colorimetry by the Duboscq method. In accuracy, it compares very favorably with that of the spectrophotometer. Readings are made in

a moment and with complete objectivity, the photoelectric cell taking the place of the technician's eye. For hemoglobin determinations, the method is unsurpassed. All colorimetric and turbidity determinations can be done with this machine. Recently, J. G. Gibson, Jr., and K. A. Evelyn⁵ have utilized the apparatus for the accurate determination of the blood volume. With this method the "Evans Blue" dye is used. Far greater accuracy is obtained with this method than with the use of congo red.

R. L. Haden⁶ recommends the use of concentration preparations of leukocytes in the study of the leukopenias. By removing the buffy coat from oxalated or citrated blood, many thousands of leukocytes are seen and the study of the blood in leukopenic states facilitated. Haden states that in the leukopenic leukemias, "sufficient cells are always found to reveal the leukemic process in the marrow." The REVIEWER would tend to disagree with the use of the word "always." Furthermore, in lymphosarcoma or other neoplastic processes metastasizing to the marrow, and in Gaucher's disease, buffy coat preparations are of no value. The method may be tried preliminary to a proposed bone-marrow biopsy.

R. L. Haden⁷ recommends the use of diffraction methods for the study of the cell diameter. In this article, he compares the Farnham's eriometer and the Pippenger blood cell tester and finds them both satisfactory. The REVIEWER prefers the more laborious, albeit more accurate, method of the calibrated micrometer eyepiece with the working out of Price-Jones curves.

J. A. Dacie and J. M. Vaughan⁸ describe a new and "quantitative" technic for estimating erythrocyte fragility. Extrinsic factors influencing fragility are the O_2 and CO_2 tension of the blood

and the temperature and pH of the hemolytic system. All blood was oxygenated in a constant manner and all procedures carried out at 96° F. (35° C.). The important factor of anemia is discounted despite recent investigations. Blood is not standardized to a constant volume which G. A. Daland and K. Worthley⁹ have demonstrated is of utmost importance.

Lead Poisoning—An important and practical study of careful methods involved in the early diagnosis of acute and latent plumbism is made by F. L. Smith, 2d, T. K. Rathmell, and G. E. Marcil.¹⁰

Symptoms—Suggestive, incipient, and definite symptoms are tabulated. Lead is excreted normally in the urine in small amounts. Marked changes occur in the red blood cell. A critical study is made of the phenomenon of stippling and of other hematological changes. A diagnostic procedure is set up in which the lead in the serum, cells, and fibrin fraction of the blood is determined in relationship to the total amount of lead in the whole blood. A careful differential leukocyte count ("hemograms and shiftogram") is also made. By means of the various procedures, the authors claim to be able to differentiate between acute, chronic, and mild lead poisoning, as well as to differentiate between mild lead toxemia and such conditions as gastroenteritis, hypercalcemia, food poisoning, sun and x-ray burns, or colics from other causes.

C. Blood Cells

Careful studies of the white cells of the guinea pig,¹¹ of the blood picture of the young rhesus monkey¹² and of the goat¹³ are made. These normal studies are of importance in the evaluation of experimental studies in the various animals.

Red Blood Cells—S. Nittis¹⁴ makes a study of the nature and the mechanism of staining of the *erythrocyte reticulum*. Simple, but important, experiments demonstrated that the reticulum forming material is a structureless protoplasmic substance, evenly distributed in the stroma of young erythrocytes, decreasing as the cell matures. Staining with brilliant cresyl blue is not permanent, and washing off occurs in the process of counterstaining. The flaky reticulum reappears when the amorphous material comes in contact with methylene blue. Nittis recommends the use of an excess of Wright's stain and of water in counterstaining. A monographic study of the relationship between the reticulocytes of the marrow and the peripheral blood in various clinical conditions is made by Magdalena Ungricht.¹⁵ M. L. Andresen and E. R. Mugrage¹⁶ studied peripheral and venous red cell values and found they could be used interchangeably after the first 3 weeks of life.

A. Alder¹⁷ makes one of the first studies in which the size of the red cells in the blood is compared with that of their progenitors in the marrow. The REVIEWER has (with H. H. Henstell) done some of this work which is important from the standpoint of understanding somewhat better the physiology of macro- and microcytosis. The younger red cells, including the reticulocytes, are always larger than the mature orthochromatic erythrocytes.

The problem of the duration of life of the red cells is discussed by E. Schiodt.¹⁸ In man, the red cells live about 30 days, but in certain pathological conditions as in congenital hemolytic jaundice, the life span becomes materially shortened. In all probability, the red cells have a definite cycle of wear and tear and finally become hemolyzed and thus destroyed. H. Wehrle¹⁹ injected

the normal nucleated red cells of the hen into the rabbit and found that active phagocytosis and intracellular digestion of erythrocytes takes place in the spleen.

J. W. Cutler, F. R. Park, and B. S. Herr²⁰ and S. M. Bouton, Jr.,²¹ analyze the influence of anemia on the blood sedimentation rate. As is well known, many investigators have concluded that anemia should be allowed for in the determination of the rate of sedimentation. From their careful studies, Cutler, *et al.*, conclude that "anemia has little to do with the phenomenon of blood sedimentation." Rapid settling is due to rapid aggregation of the red cells; in turn, this is due to a factor in the plasma. The 3 phases of sedimentation—aggregation, sedimentation, and packing—should be discriminated by the use of a chart. Bouton maintains that attempts at "correction" of the sedimentation rate by compensating for anemia, and especially by the use of "conversion charts," represent "pseudoaccuracy and in large part invalidate the readings."

On the other hand, M. Hynes and L. E. H. Whitby²² confirm the careful work of M. M. Wintrobe and J. W. Landsberg²³ regarding the necessity for using a correction factor when dealing with a case in which anemia is present. F. Lee²⁴ describes a photographic method ("sedimentometer") for determining the sedimentation rate; multiple readings, as Cutler and others have suggested, can be made. C. Lintgen and K. Fry²⁵ studied the sedimentation rate in acute appendicitis and acute pelvic inflammation. 10 per cent of the patients with the latter condition presented a normal rate whereas 48 per cent of the patients with acute appendicitis had normal rates. The test could not be relied upon to distinguish between the 2 conditions. It should be remembered that an increased sedimentation rate is merely another indi-

cation that a given patient is *ill*. It has no more (or less) significance than an increased pulse rate or fever or leukocytosis. Woe to the clinician who must rely upon a single laboratory test to tell him whether he is dealing with appendicitis or acute intestinal obstruction! *All* the factors (clinical as well as laboratory) in a given case must be taken into account.

White Blood Cells—C. A. Doan²⁶ studied the response of the leukocytes to hyperpyrexia induced by the Kettering Hypertherm and found that a majority of the cells making up the postfebrile leukocytosis is composed of young polymorphonuclears. This type of response may differ materially from that induced by malaria, in which monocytosis is marked. The latter response, as Breutsch has suggested, may be a more valuable one. K. Kornblum, F. Boerner and S. G. Henderson²⁷ studied the changes in the formed elements of the blood following therapeutic x-radiation. They found that this procedure did not induce anemia. The leukocyte count is almost always lowered, particularly so with the lymphocytic group; within 5 to 8 weeks, the leukocyte count should become normal. It is inadvisable to permit the leukocyte count to drop below 1000 per cu mm. The authors recommend frequent complete blood counts during the course of x-radiation. Much has recently been written of the "leukopenic index," a test which has been enthusiastically received by allergists as another test indicating hypersensitivity to various foods. Vaughan and others who have written on the subject claim that reduction of 1000 or more leukocytes after taking food is due to a direct allergic effect upon the marrow. The careful and critical studies of J. M. Hill and E. B. Nethery²⁸ indicate that several factors, including that of physiological redistribution of leukocytes, in-

adequate sampling, and technical errors may cause variations in count in excess of 1000 leukocytes. A plea is made for more critical evaluation of this method, which is subject to so much misinterpretation.

Leukocytosis of Acute Inflammation—An important study of the mechanism of the leukocytosis of acute inflammation is made by A. Nettleship.²⁹ An intracutaneous inflammation was induced in rabbits by the injection of streptococcus hemolyticus and polymorphonuclear leukocytosis was induced. Necrosis of the cytoplasm of leukocytes "infiltrating" the injured area with resultant release of substances from their cytoplasm is thought to be the cause of the general leukocytosis. Another study of the mechanisms resulting in leukocytosis (and of leukopenia) is made by F. Faludi.³⁰ He concludes that every form of polymorphonuclear leukocytosis derives from the marrow and that there is no evidence of a splanchno-peripheral combination (redistribution) of leukocytes.

Familial "shift to the left" (*i e*, the familial and congenital presence of immature polymorphonuclears) is now called the Pelger syndrome. E. Undritz³¹ made studies of the blood and marrow changes in this condition and describes a subdivision of the syndrome. Those interested are referred to the original articles.

Sulfanilamide Reactions

The great interest and the tremendous use of sulfanilamide in the last 2 years has naturally led to interest in the various reactions which not infrequently occur with this drug. Cyanosis is common; although in some cases either met- or sulfhemoglobin has been demonstrated, in others, the nature of the definitely inactive pigment has not been determined. H. E. Archer and G. Discombe³² state that the development of sulfhemoglobinemia

can be prevented or delayed by keeping the colon empty by enemata, by giving the patient a low residue diet without eggs, and by using large doses of liquid petrolatum. I. Posner, N. W. Guthrie and M. R. Mattice³³ studied the abnormal blood pigment after sulfanilamide therapy. Methemoglobinemia was transient and quickly disappeared when therapy was withdrawn, but sulfhemoglobinemia might persist for weeks. When the hemoglobin level is low, sulfanilamide administration must be undertaken cautiously. In any event, the appearance of definite cyanosis is a signal for at least temporary cessation of therapy; in anemia, the warning signal of cyanosis may be absent. L. C. Chesley³⁴ failed to find inactive hemoglobin pigments in 8 patients who had developed cyanosis with sulfanilamide. In the REVIEWER's experience, sulf- or methemoglobin may be demonstrated only in about one-third of the cases developing cyanosis; other inactive pigments might, however, be present, these could be demonstrated by more exact methods. Following the development of inactive pigment, excretion must take place, this results in icterus of slight degree and is followed by a compensatory reticulocytosis. Anemia of moderate degree may develop and acute hemolytic anemia will occasionally ensue. This is characterized by well-marked anemia, slight icterus, and polymorphonuclear leukocytosis. Marked immaturity in erythrocytes with the appearance of nucleated red blood cells is an indication for the cessation of therapy, according to G. H. Jennings and G. Southwell-Sander.³⁵

Agranulocytosis may occasionally develop, although leukopenia is more common. C. J. Young³⁶ reports a case of agranulocytosis in a man who had been given the drug in dosage of 3 Gm. daily for 18 days. The reported cases of agranu-

locytosis have generally occurred in individuals who have taken large doses of the drug for 2 to 4 weeks, and who have been unsupervised by much medical attention or by leukocyte counts. C. J. C. Britton and J. Howkins³⁹ studied the leukocyte and differential counts in 50 ambulatory individuals receiving sulfanilamide therapy (0.5 Gm. daily for 14 days). In 14 cases, a definite, though slight, polymorphonuclear leukopenia developed (5000 to 3000 w. b. c.), usually in the third week. Eosinophilia developed in 7 cases. J. A. Bigler³⁸ studied the leukocyte response in 33 cases (1 Gm. of the drug for every 20 lbs. was given daily). Leukocytosis usually diminished with use of the drug.

ANEMIA

As the result of the studies of Wintrobe, Haden, Osgood, and the REVIEWER,⁴⁰ the concept that the anemias are best classified physiologically and with reference to the predominant cell size has gained ground. Dameshek brings out that there is no "primary" anemia, that all anemia is symptomatic and "secondary" and therefore that both designations are best dropped. The various pathologicophysiological mechanisms in producing anemia are discussed and the combination of dietary, gastrointestinal and other factors in various cases is pointed out. Sharp distinctions are drawn between the microcytic (usually iron deficient) and the macrocytic (often liver-extract deficient) types of anemia.

Chronic Iron Deficiency States (Chronic Hypochromic Anemia)

The designations "primary" and "idopathic" for those cases of chronic iron deficiency in middle-aged women in which bleeding and malignancy are not factors probably are best discarded. The

iron deficiency state commonly occurs in women of the very poor economic groups; much of it is due to inadequate consumption of iron-containing foods. However, of 100 women on the same type of poor diet, only a certain percentage⁴¹ will develop anemia. If these are thoroughly investigated, they will usually be found to have achlorhydria, although others will have had multiple pregnancies, hemorrhagia, etc. It is always important in these cases to attempt to ferret out various etiologic possibilities. This has been done by S. G. Meyers, A. H. Price, L. J. Foster, and E. A. Sharp,⁴¹ who stress the gastrointestinal, gynecologic, endocrine, and psychiatric features. One-fourth of their patients fell into the class of "constitutional psychopathic inferiority", they often have a capricious appetite and usually dislike meat. W. M. Fowler and A. P. Barer⁴² emphasize the importance of even the normal menstrual flow as the cause of a serious drain on the iron stores, thus leading to anemia when associated with certain other abnormalities. They found no evidence of a faulty iron metabolism. A. Chappell and L. Bivings⁴³ found that the majority of a large group of pregnant colored women developed increasing hypochromic anemia as gestation progressed. Peculiarly enough, there was little or no response to iron, although the anemia could be prevented or even improved by the administration of *cod liver oil*.

Treatment—As regards treatment of the chronic iron deficiency state, only 1 medication need be considered, and that is *iron*. As P. F. Hahn and G. H. Whipple⁴⁴ state, "No investigator has reported any condition of copper deficiency in man or dog. It is unlikely, therefore, that in . . . the various anemias of man, any significance attaches to the intake of copper." The same may be said for liver extract either singly or in

combination. To use the special combinations of iron with liver extract, gastric extract, vitamin B, *etc.*, is to increase the cost to the patient without other benefit. W. H. Barker and D. K. Miller⁴⁵ studied the Whipple "secondary anemia fraction" in 11 cases of hypochromic anemia and obtained a reticulocyte response with this medication, although responses in hemoglobin were absent or questionable. There was no question, however, about the effects of inorganic iron. Large amounts of mucus are commonly found in the gastric juice of cases of chronic iron deficiency. C. W. Heath, G. R. Minot, F. J. Pohle, and G. Alsted⁴⁶ found that large amounts of mucin when administered together with small doses of iron caused inhibition of absorption from the bowel. R. L. Haden⁴⁷ presents a fascinating paper on the historical aspects of iron therapy in anemia. Emphasis is placed upon Bland's prescription and his advocacy of the use of large dosage.

The Liver Extract Deficiency State (Pernicious Anemia)

H. A. Magnus and C. C. Ungley⁴⁸ studied the gastric mucosa fixed soon after death from 7 cases of pernicious anemia. In all the cases the upper two-thirds of the stomach showed such severe atrophy that this area was reduced to the thinness of parchment. The lower one-third of the stomach was of normal thickness. They conclude that the gastric lesion is not the result of inflammation but must be regarded as an atrophic process, possibly congenital. W. Richardson⁴⁹ reports a case of pernicious anemia following enteroenterostomy; the condition cleared up following reoperation. It is important to remember that various short-circuiting operations may result in chronic deficiencies in iron, vitamin B, or the liver extract principle. A. Bianco

and N. Jolliffe⁵⁰ found that alcohol addicts tended to show macrocytosis of the red cells; the cause of this was not determined (was it gastric or hepatic in origin?). A case of pernicious anemia in the negro is reported by J. Millett.⁵¹ This occurrence is rare. The majority of the patients are of the blond, Nordic variety. Friedlander some years previously found that of 500 cases, 3 were in negroes. Millett found only 64 reported cases of the disease in negroes.

E. Jones⁵² points out that patients with pernicious anemia have usually lost considerable weight when they are first seen. The rapid gain in weight following liver therapy is cited and it is suggested that there may be a factor or factors present in liver extract, aside from the hematopoietic principle, which may play a part in the weight changes. R. H. Kampmeier and E. Jones⁵³ describe 3 cases of pernicious anemia with optic atrophy, which they believe is due to an intrinsic degenerative process. This lesion has responded well to specific therapy.

H. I. Goldstein⁵⁴ states that "it is indeed regrettable that our American writers and workers . . . have failed to give due credit to the pioneers and early workers with liver therapy in anemia." Goldstein has unearthed a number of references antedating Minot and Murphy's contribution in which the use of liver is recommended. This criticism is doubtless correct, but it must be admitted that the first definite, convincing, and scientifically controlled investigation proving the effect of liver in cases of pernicious anemia undoubtedly is that of Minot and Murphy. U. Uotila⁵⁵ found that extracts of various parts of the small intestine had very definite antianemic potency. Although the pyloric portion of the stomach had the greatest unitage of potency, the *total amount* of hematopoietic principle found in the small intestine was far greater than

in the relatively small amount of gastric tissue. Uotila concluded from these studies that the small intestine probably plays an important rôle in the active formation of antianemic principle and that Castle's conception that the "intrinsic substance" was formed *only* in the stomach was probably incorrect.

Treatment—For some time, there has been much dissatisfaction with the labeling of the liver extracts, particularly of the parenteral type. The vials are labeled according to the amount of liver from which the extract was derived, and not in terms of potency of the contained extract. The U. S. Pharmacopeia, in instituting an antianemia preparations advisory board, has performed an excellent service. Extracts are now labeled in terms of "units." A unit is that amount of liver extract which, when given daily (either orally or parenterally) produces an adequate reticulocyte and erythrocyte response. The dilute extracts contain 1 to 2 units per cc (parenteral), some concentrated extracts are said to contain as high as 15 to 20 units per cc. Standards for maximum reticulocyte responses to intramuscular liver therapy are given by R. Isaacs and A. Friedman.⁵⁶

Most observers now recommend the use of *parenteral liver therapy*. With the use of regular injections of a potent extract, there need be no question regarding absorption. The patient is furthermore left under systematic observation. Neurological lesions can be prevented from occurring if sufficient parenteral liver is given. The treatment of the neurological lesions, when present, is apt to be difficult and may require far larger dosage of liver extract than is necessary to obtain merely a good hematological response. In a severe neurological case, injections may well be given *daily* for several weeks, then 3 times weekly, then twice weekly, *etc.* These should be given

without recourse to the erythrocyte count, the main emphasis being placed upon the neurological lesions. With vigorous treatment of this sort, definite results may be expected. A return to normal of the vibration sense, a diminution or even complete absence of ataxia, in-co-ordination, bladder symptoms, hyperesthesias, *etc.* The lateral column lesions (spasticity, positive Babinski, *etc.*) are more difficult to treat, but even these respond somewhat to continued treatment. A good result may require patient and persistent therapy for a year or more.

Deficiency Syndromes, Usually Associated with Macrocytic Anemia

The importance of adequate nutrition with relation to the anemias has been stressed in recent years. As the result of numerous researches, it is now seen that such disorders as pernicious anemia, sprue, pellagra, polyneuritis and combined system disease are closely related. Most of these disorders probably have much to do with vitamin B deficiency, which appears to be the central element at fault in these cases. In certain syndromes, one fraction of the vitamin B complex may be at fault, and in others, another fraction. Thus, in pellagra, nicotinic acid has been shown to be the P-P factor of Goldberger and startling results have been obtained by the use of this relatively simple chemical in the treatment, particularly of the mucous membrane lesions of the disease. The use of nicotinic acid in pellagra dates from the researches of C. A. Elvehjem, R. J. Madden, F. M. Strong, and D. W. Woolley.⁵⁷ These experimental studies were rapidly taken up and confirmed in clinical work by T. D. Spies, C. Cooper, and M. A. Blankenhorn⁵⁸ and D. T. Smith, J. M. Ruffin, and S. G. Smith.⁵⁹ R. S. Matthews⁶⁰ reports on the treatment of 16 cases of pellagra with nico-

tinic acid. This was given either orally or intravenously. The average oral dosage was 100 to 200 mg t i. d., and the intravenous injections were given in 1 per cent aqueous solution in dosage up to 100 mg. There was prompt and dramatic response, particularly in the symptoms referable to the gastrointestinal tract and psychiatric symptoms. Matthews felt that nicotinic acid was not therapeutically effective against the peripheral neuritis which was often associated with pellagra nor did it influence directly the condition described as "central neuritis." These conditions were helped by vitamin B₁ in large doses given intravenously and intraspinally.

P. J. Fouts, O. M. Helmer, S. Lepkovsky and T. H. Jukes⁶¹ produced hypochromic microcytic anemia in puppies on a diet deficient only in the B₆ principle (the B₂ complex contains at least the following: Nicotinic acid, riboflavin, B₁, and B₇ (weight-maintaining and weight-gaining factors) and the rat-antidermatitis factor or B₆). When the B₆ principle was given to these deficient, anemic puppies, striking reticulocyte and erythrocyte responses took place. These and other researches of similar type in monkeys and birds may have a definite clinical bearing in certain cases of anemia, and perhaps even in pernicious anemia and sprue.

F. M. Hanes⁶² does an excellent service by publishing Ashford's extensive bibliography of sprue. Although Ashford erroneously believed that the *Mompha pilosus* was the causative agent of the disease, nevertheless his pioneer work on the subject must always remain as one of the classical series of investigations in tropical medicine. Sprue (like pernicious anemia) is a deficiency disease, dependent upon dietary, gastrointestinal, and other less well-defined factors.

Possibly related to the anemias of vitamin deficiency, possibly to some other mechanism which has to do with *utilization* of active principle, by the marrow is the "achrestic-type" anemia described by M. C. G. Israels and J. F. Wilkinson.⁶³ Here, one is dealing with a condition which is in every respect identical with pernicious anemia but which fails to respond to liver extract. Whether or not such an entity is present is debatable. The REVIEWER has, however, seen occasional typical examples of the disease with refractoriness to liver therapy. This is particularly true of the "pernicious anemia of pregnancy," in which it often is necessary to give transfusions as well as liver extract. The association of macrocytic anemia with hepatic disease has received much attention. At first, the ready assumption was made that liver deficiency due to the abnormal state of the liver was the cause of macrocytosis. Certain observations appeared to bear this out, but recently many doubts have been cast on this, apparently too simple, explanation. Thus L. Schiff, M. L. Rich and S. D. Simon⁶⁴ made extracts from the livers of 5 cases dying of severe hepatic disease, in 3 of whom macrocytic anemia was present and injected them in patients with pernicious anemia. Typical reticulocyte and erythrocyte responses were induced in all cases. The conclusion was "that the macrocytic anemia associated with liver disease is not caused by failure of the liver to store the specific anti-anemic substance."

Aplastic Anemia

Occasionally, the marrow becomes more or less destroyed and fatty because of the action of various chemicals, possibly because of other unknown factors. The term "aplastic anemia" should be reserved for those conditions in which marrow growth has become greatly, if

not totally, diminished. This will result in progressive anemia, leukopenia, marked reduction in polymorphonuclears, very low reticulocyte count and almost complete absence of platelets. The REVIEWER objects to the use of the designation of "aplastic anemia" for those cases presenting anemia, leukopenia, and thrombocytopenia which are associated with a "full" marrow. These are "pseudoaplastic" and should be discriminated from the true aplastic forms. C. P. Rhoads and D. K. Miller,⁶⁵ on the other hand, divide their cases of "aplastic anemia" into various groups: (a) With aplastic marrow, (b) with hyperplastic marrow, (c) with active marrow; (d) with megakaryocytic marrow, (e) with sclerotic marrow. It seems to the REVIEWER that these observers have grouped together all sorts of conditions, including myeloid leukemia, under one heading. The differences in picture are probably due to differences in disease rather than to variation in picture. A similar misconception is seen in the article of E. A. Gall,⁶⁶ who reports a case of benzene poisoning (called aplastic anemia) with "bizarre extramedullary hematopoiesis." The blood picture and the so-called metaplasia in various organs seem quite typical of leukemia. M. Kadin⁶⁷ reports 3 cases of aplastic anemia following the use of neoparsphenamine

Hemolytic Anemia

W. Dameshek and S. O. Schwartz⁶⁸ reported 3 cases of acute hemolytic anemia which failed to respond to transfusions but which were dramatically cured by splenectomy. In Cases 2 and 3 active serum isohemolysis was discovered which were capable of hemolyzing red blood cells of all blood groups, including those of Group O. In the third case, there was marked spherocytosis and increased fragility of the red cells, both

of which characteristics have been supposed to be characteristic of congenital hemolytic icterus. As this patient improved, spherocytosis and increased fragility gradually diminished and then returned to normal, coincidentally with diminution in titer of circulating hemolysin. This led to the speculation that the spherocytosis was *due* to the action of lysis. Animal experimentation by the same authors⁶⁹ demonstrated that such was the case. By varying the dosage of hemolytic serum various hemolytic syndromes could be reproduced at will together with the associated spherocytosis and increased fragility. Numerous experiments demonstrated that these changes were not due to bone-marrow disease but to changes produced by the lytic agent. It was concluded that all the various hemolytic syndromes were probably the result of the activity of various types of hemolysins. The acquired cases may be acute, subacute, or chronic. The acute types are frequently not as benign as some observers appear to think, and do not necessarily respond to transfusions, but may require splenectomy as an emergency measure. Current misconceptions about this condition are well brought out in an article by H. M. Greenwald,⁷⁰ who states, "Obviously, splenectomy performed on a patient suffering from acute hemolytic anemia of the Lederer type would be calamitous." In 5 successive cases observed by the REVIEWER, dramatic recoveries took place when splenectomy was done. E. H. Baxter and M. W. Everhart⁷¹ suggest that infection and allergy should be considered as causative factors. M. C. G. Israels and J. F. Wilkinson⁷² report 4 adult patients suffering from hemolytic jaundice, all of whom had splenectomy. The spleens in all cases showed reticulum-cell proliferation, differing greatly from that seen in the congenital types. The authors cannot explain

the spherocytosis and increased fragility, which, in common with numerous investigators, they have considered to be pathognomonic of the congenital type. Recently, several interesting cases of paroxysmal nocturnal hemoglobinuria have been reported^{73, 74, 75} Ham and Dacie, *et al.*, concluded that the nocturnal hemolysis with hemoglobinuria might be explained by changes in the pH of the blood to the acid side during the night and by somewhat abnormally sensitive cells. The article of Scott, *et al.*, is distinguished by excellent clinical and pathologic descriptions. H. W. Josephs⁷⁶ described an antilytic factor in normal serum and ascribes the often dramatic effects of transfusions to this factor. Extracts of protein-free plasma made from the ether-insoluble fraction have thus far been of some value in the treatment of chronic hemolytic states.

Anemia after the excessive use of vitamin A was produced in rats by W. Papke,⁷⁷ who states that various reactions including anemia might be due to the administration of large doses of this substance. J. Caffey⁷⁸ describes the roentgenological changes of erythroblastic (Cooley's) anemia. The anemia of nephritis, which becomes worse as the disease progresses, is still mysterious in its etiology. S. R. Townsend, F. Massie, and R. H. Lyons⁷⁹ claim that a correlation exists between the decreased renal function, the development of normocytic anemia, and the development of a diminished secretion of free hydrochloric acid in the gastric juice. The latter factor possibly interferes with the proper metabolism of ingested food as well as in the absorption of iron. M. M. Braverman⁸⁰ describes the anemia of pulmonary tuberculosis from a study of 509 cases. Most commonly, hypochromia and microcytosis are present and *iron* is of some value

DISORDERS OF THE WHITE CELLS

Infectious Mononucleosis

This is a common infectious disease which frequently is overlooked. It is characterized by fever, sore throat, headache, lymphadenopathy, and often splenomegaly. In some cases, the liver becomes enlarged; rashes may occur; purpura may develop, abdominal pain may be outstanding. More often than not, the case is "atypical" and the diagnosis is not made until (a) the condition is considered, (b) the generalized lymphadenopathy discovered, (c) the blood smear examined. Confirmatory evidence is then sought with the heterophile agglutination test.

The etiology of the disease remains unknown, although one investigator⁸¹ continues to find an organism of the *Listeria* group in some of her cases. She states that these organisms are often overlooked because of difficulty of cultivation. Israel Davidsohn⁸² continues his work on the heterophile agglutination test and gives methods for differentiating between a positive reaction due to the disease and that due to serum sickness or associated states. B. Hatz⁸³ points out that the Wassermann reaction may occasionally be positive in the condition, disappearing with the disappearance of the positive heterophile agglutination reaction. This points to a similarity in the mode of formation of the antibodies concerned.

V. Schmidt and A. Nyfeldt⁸⁴ described meningoencephalitis in a case of infectious mononucleosis and were able to grow a *Listeria* organism from the spinal fluid. The difficulty in differential diagnosis between this condition and acute leukemia is stressed by H. J. Ustvedt.⁸⁵ This author advises sternal puncture as a diagnostic measure. The REVIEWER

has thus far failed to find this procedure necessary in a given case. In infectious mononucleosis, quite in contrast with acute leukemia, the cells are exceedingly variable in size, shape, and staining characteristics. There is furthermore no anemia or reduction in blood platelets.

Agranulocytosis

This disorder seems to be diminishing in incidence, possibly because physicians have learned of the possible dangers of amidopyrine, dinitrophenol, and other drugs which may cause the disease. An allergic reaction on the part of some individuals is probably at the basis of the disorder, as demonstrated not only by statistical methods but experimentally by W. Dameshek and A. Colmes.⁸⁶ Occasionally, reactions to the arsphenamines occur and in an individual who shows reactions to these drugs, one should not continue treatment until the leukocyte count has been investigated. R. V. Rajam and R. B. Tampr⁸⁷ encountered 3 cases of blood dyscrasia in treating 18,620 cases of syphilis. A. Lieberman and A. Weiss⁸⁸ point out that the earliest change is a reduction in the polymorphonuclear cells. If this stage is recognized, the patient may be spared the irreversible change of agranulocytosis or aplastic anemia. The relation of drug therapy in general to the neutropenic states is ably discussed by R. R. Kracke,⁸⁹ who was one of the first to bring out this relationship. A chart is presented in this article which demonstrated the practically complete disappearance of agranulocytosis from Denmark after the importation of amidopyrine was prohibited. A large number of proprietary preparations containing amidopyrine is listed. Eleven cases of agranulocytosis following the use of sulfanilamide are cited. Paul Reznikoff⁹⁰ points out that 4 factors are important in the causation of the disease

Fatigue; drugs, menstruation, and infection. Chronic fatigue and insomnia were of frequent occurrence. Surgical procedures will occasionally result in marked leukopenia, if not in outspoken agranulocytosis. J. Van Duyn, Jr.,⁹¹ discusses the "leukocyte exhaustion" which may follow surgical procedures, particularly those associated with paralytic ileus. Liver extract and transfusions of blood appeared to be of definite therapeutic value in these cases.

The therapy of this condition remains unsatisfactory. The advocacy of such varied remedies as *liver extract, transfusions, x-ray therapy, pentose nucleotides, adenine sulfate, yellow bone-marrow extract, etc.*, indicate the lack of a specific medication. H. E. Bock⁹² *transfused blood from a case of chronic myelogenous leukemia* to a patient with agranulocytosis, recovery occurred. Bock estimated that the quantity of blood used in the 14 transfusions was equivalent in white cells to that provided by 250 transfusions of ordinary blood. C. M. Marberg and H. O. Wiles⁹³ gave an extract of yellow bone-marrow to 4 patients with leukopenia and 6 with agranulocytosis, all recovered. Critical examination of these cases reveals that many therapeutic agents were usually used and that several of the cases are doubtful ones. The best therapy at hand at present seems to be the derivatives of nucleic acid in the form of pentose nucleotides or adenine sulfate. There seems to be no rational value for the use of transfusions.

Leukemia

The articles on leukemia seem to increase, even though knowledge regarding the causes and cure of this condition remains minimal. S. Oliver and B. Katzman⁹⁴ claim that leukocytosis may occasionally develop into leukemia. They

conclude that "leukocytically produced noxae cause a defensive hypertrophy of a certain hematopoietic system, which in turn may be the basis for a leukemia." Most observers conclude, however, that leukemia is neoplastic. T. S. Evans⁹⁵ cites the evidence in this regard, including the cases of leukemia associated with leukocytic neoplasms. S. N. Ardashnikov⁹⁶ studied the genetics of leukemia in man based on 33 pedigrees. Environmental causes were lacking, but the familial cases reported in the literature point to a "conditionally dominant autosomal type of inheritance," especially in the lymphatic form of leukemia.

Monocytic leukemia continues to be of interest. Despite the many and well-studied cases reported, some investigators continue to be skeptical of this third type. Regena C. Beck⁹⁷ cites the importance of supravital studies in the differential diagnosis of the cell type in these cases. Good illustrations are given. M. S. Sacks⁹⁸ describes systemic proliferation of the reticuloendothelial system (reticuloendotheliosis). Excellent descriptions and photographs of the pathological material are given.

B. S. Leavell⁹⁹ studied the incidence and factors influencing the duration of life in chronic leukemia. Studies made from 3 large hospitals indicate that the incidence of leukemia is increasing, although no definite statement in this regard can be made because of better standards of diagnosis. The average duration of life after onset of symptoms was 3.2 years in 87 patients with chronic myelogenous leukemia and 3.6 years in 49 patients with chronic lymphatic leukemia. The duration of life was slightly longer in those patients with relatively low leukocyte counts.

The retinal changes in leukemia are discussed by G. G. Gibson,¹⁰⁰ who cites the early darkening of the veins, hemor-

rhages, and the occasional edema of the disk. An interesting study is presented by L. A. Erf and A. Fine¹⁰¹ on serial blood and bone-marrow findings of an 8-month premature and its roentgen-ray treated chronic myeloid leukemic mother. The offspring of this leukemic mother was normal and remained so during the 7 months of observation.

Treatment — Nothing new has appeared in the treatment of leukemia, either acute or chronic. R. E. Fricke and C. H. Watkins¹⁰² recommended *radium* in cautious, limited dosage, particularly for the atypical aleukemic types. There is something to be said for this method, since undertreatment rather than drastic treatment is stressed. Too frequently, one sees a patient made more sick by his treatment than by his disease. Oftentimes, the longest duration of the disease is seen in those cases which have received no treatment whatever. In the acute types, x-ray therapy should be avoided. **Transfusions** might be given as a temporary measure.

Leukocytic Neoplasms

An excellent article on giant follicular lymphadenopathy is presented by D. Symmers.¹⁰³ This condition, characterized by lymphadenopathy, relatively benign, prolonged course, sensitivity to x-ray therapy, and the presence of giant follicle hyperplasia of the biopsied lymph node was first described by the Mt. Sinai investigators Baehr, Rosenthal, and Klemperer. Symmers points out that this condition is capable of direct transformation into a hitherto undescribed polymorphous cell sarcoma. Hodgkin's disease may be simulated. Certain cases of lymphadenopathy with "necrotic folliculitis" may be a phase in the evolution of this disease.

Plasma cell myeloma ("multiple myeloma") is reported in 2 cases with survivals of 6 and 10 years.¹⁰⁴ X-ray

therapy was of distinct benefit in relieving the bone pain. The impression was obtained that if the x-ray picture is that of a giant cell tumor but the histology that of plasmacytoma, the condition is relatively benign. The hyperproteinemia of multiple myeloma has always proved of great interest and continues to be reported, *viz.*, A. E. Feller and W. M. Fowler.¹⁰⁵ "The fact that hyperproteinemia and hyperglobulinemia are practically limited to multiple myeloma may be useful in differential diagnosis of multiple lesions involving skeletal system."

Lymphosarcomatous involvement of the lungs is reported by E. H. Falconer and M. E. Leonard.¹⁰⁶ Pulmonary involvement was present in 36 per cent of the cases of lymphosarcoma, in 30 per cent of their cases of lymphatic leukemia and in 31 per cent of the cases of Hodgkin's disease. Mediastinal involvement in Hodgkin's disease is discussed by C. B. Wright¹⁰⁷ and by H. Z. Kasabach and K. R. McAlpin.¹⁰⁸ In the latter's cases, 77 of 251 patients had mediastinal involvement, usually in addition to evidence of disease elsewhere. It was felt that the maintenance of the patient's weight and general well-being is stressed as an important factor in prolongation of life.

HEMORRHAGIC DISORDERS

The hemorrhagic disorders may be classified as follows:

A. *Those Associated with Platelet Deficiency (Thrombocytopenic Purpura)*

1. Secondary thrombocytopenic purpura (leukemia, aplastic anemia, other destructive processes of the bone marrow)
2. Primary thrombocytopenic purpura (purpura hemorrhagica)

B. *Those Associated with a Clotting Defect*

1. Hemophilia
2. Pseudohemophilia
3. Prothrombin and vitamin K deficiency (severe jaundice)

C. *Those Associated with a Vascular Defect (Vascular Purpura, Nonthrombocytopenic Purpura, Anaphylactoid Purpura, etc.)*

Due to infectious, allergic "toxic," menstrual, and other conditions causing increased capillary permeability

A. Thrombocytopenic Purpura

Usually the "primary" or idiopathic form is discussed under this heading. Many cases of this type are, however, erroneously classified as such when in reality the platelet deficiency is due to destruction of the marrow by a process such as leukemia or malignant disease. In these cases, marked anemia, usually of the normo- or macrocytic variety, is present and there are also changes in the leukocytes, usually leukopenia. In thrombocytopenic purpura of the idiopathic variety, however (purpura hemorrhagica), there is very slight if any anemia (which is of the hypochromic, microcytic variety) and the leukocyte count is usually elevated in response to hemorrhage.

Etiology—The cause of the "idiopathic" form of thrombocytopenic purpura has not been demonstrated. A megakaryocyte abnormality in the bone marrow has been postulated. H. Fleischhacker¹⁰⁹ states that in this condition the megakaryocytes are increased and younger forms are present. The cause of this increase is in doubt. T. L. Squier and F. W. Madison¹¹⁰ studied 3 patients in whom drug allergy, toxic changes, and hematopoietic disease could be excluded. They observed a depression in platelets following ingestion of certain foods. The exclusion of suspected foods from the diet was followed by striking clinical improvement. They suggest the value of allergic investigation of these patients. Occasionally, thrombocytopenic purpura may be the outstanding feature and pos-

sibly the first symptom of acute, disseminated lupus erythematosus¹¹¹

Treatment—In the treatment of this disease, various medications and procedures have been suggested. The value of *splenectomy* has been often demonstrated and remains the treatment of choice in the severe case. In fulminating purpura, the response to splenectomy is one of the most dramatic things in medicine. H. W. Jones, L. M. Tocantins, and R. M. Smith¹¹² examined the procedure of splenic irradiation and concluded that it was not a satisfactory method of treatment, although it might be used in selected cases. They recommend various procedures, chiefly *transfusions*; splenectomy is deprecated. Various authors recommend the use of intravenous ascorbic acid (vitamin C), but in the experience of the REVIEWER, this has had absolutely no effect either on the platelet count or the bleeding tendency. In the mild case, one may temporize with *diets, vitamins, splenic irradiation, etc.*, but when faced with a severe case to temporize may be disastrous.

B. Hemorrhagic Diseases with a Clotting Defect

The outstanding example of the hemorrhagic diseases in which a clotting defect is present in the plasma is hemophilia. The missing clotting factor probably resides in the globulin fraction of the plasma, as pointed out by A. J. Patek, Jr., and F. H. L. Taylor¹¹³. Attempts to influence the clotting time over a prolonged period of time by the injections of this globulin fraction have hitherto been unsuccessful. However, F. J. Pohle and F. H. L. Taylor¹¹⁴ were able to prepare from beef plasma globulin substance which was immediately effective in controlling hemorrhage from traumatized bleeding lesions in hemophiliacs. The globulin substance in dried form placed

in contact with the bleeding site proved especially effective in allowing unrestricted dental extraction in these cases.

Rarely, extensive bleeding takes place from a lack of fibrinogen in the blood. This has been called "pseudohemophilia." R. G. Macfarlane¹¹⁵ described a boy with no fibrinogen; a definite family history was present.

One of the outstanding advances in the past year has been that associated with the accumulation of evidence regarding the state of *prothrombin deficiency* which is not infrequently associated with severe jaundice. The principles of testing for the prothrombin clotting time have been laid down by A. J. Quick, M. Stanley-Brown and F. W. Bancroft.¹¹⁶ The blood is oxalated and the plasma obtained. The plasma is mixed with an emulsion of dried rabbit brain to supply an excess of thromboplastin and then calcium chloride is added to the mixture (*i. e.*, everything is supplied to the plasma but prothrombin). The number of seconds it takes for this mixture to clot depends solely upon the prothrombin present—since the mixture contains thromboplastin, calcium, and fibrinogen. Normal values range from 15 to 25 seconds. With prothrombin deficiency, the clotting time of the mixture goes up to 30, 40, 50, or more seconds. E. D. Warner, K. M. Brinkhous, and H. P. Smith¹¹⁷ describe more exact methods for determining prothrombin. The prothrombin deficiency can be described in terms of percentage—*i. e.*, if a normal prothrombin clotting time is called 100 per cent, the percentage of prothrombin decreases as the prothrombin clotting time is increased. With a marked reduction in the prothrombin level of the blood, bleeding will usually occur, especially in response to operative procedures.

One of the most interesting correlations which has appeared is that existing

between the prothrombin coagulation time and the degree of *vitamin K* saturation within the body. A bleeding tendency was observed in chicks fed on a deficient diet. H. Dam¹¹⁸ and H. J. Almquist and E. L. R. Stokstad¹¹⁹ identified the deficiency factor as a new fat-soluble vitamin, which has been designated the antihemorrhagic vitamin, or vitamin K. Dogs with chronic jaundice due to biliary fistula develop a prothrombin deficiency which, according to H. P. Smith, E. D. Warner, K. M. Brinkhous, and W. H. Seegers¹²⁰ is due to faulty absorption of vitamin K from the intestine. Bile is necessary in this regard. Upon the addition of large amounts of vitamin K concentrate derived from dry alfalfa meal or from putrefying fish meal, there was a reversal in the bleeding tendency and a reversion to normal of the prothrombin clotting time. The clinical applications of these important findings are discussed fully in one of the issues of the Mayo Clinic Proceedings.¹²¹ A. M. Snell concludes here "that the hemorrhagic state in jaundice is attributable to a deficiency in prothrombin which in turn is due to failure of absorption or utilization of some substance normally present in the diet which requires bile for its absorption, this substance may be vitamin K." H. R. Butt and A. M. Snell further state that the administration of this vitamin together with bile or bile salts to jaundiced patients has reduced elevated prothrombin times and has probably prevented unusual bleeding. To operate on a patient with *chronic jaundice* is serious business and requires adequate preparation with *calcium, transfusions, bile by mouth*, and very likely *vitamin K*. K. M. Brinkhous, H. P. Smith and E. D. Warner¹²² describe cases in which these procedures have been used with gratifying effect. The vitamin K is given in the form of a fat-soluble alfalfa extract, pre-

viously tested for its potency. This material is now being prepared for commercial distribution.

C. Hemorrhagic Disease Associated with a Capillary Defect

Increased capillary permeability is present in many conditions and is associated with increased bleeding from mucous membranes, ecchymotic spots, and petechiae. The "devil's pinches" so commonly seen in women represent one of these phenomena. E. C. Smith¹²³ recommends the use of estrogenic preparations, eradication of foci of infection, and a good diet. Vitamin C has been found inadequate in these cases. Now, a closely related substance, vitamin P, is being recommended.¹²⁴ Vitamin P in the form of daily intravenous injections of 50 mg of *citrin* was given in a case of Schoenlein-Henoch purpura. It was thought that vitamin P might regulate the permeability of the capillaries. *Moccasin snake venom* continues to be used with varying success. Increasing doses of this preparation may diminish capillary permeability in such cases as chronic episaxis and hereditary hemorrhagic telangiectasis.

Transfusions — The use of transfusions has been increasing rapidly. The necessity of careful typing and cross-typing is stressed by the RIAIWER in a recent communication based upon 5 severe transfusion reactions, 4 of them fatal.¹²⁵ The following statements are made: "Blood typing preliminary to transfusion carries with it a definite sense of responsibility and can never be done too carefully. Both typing and cross-matching should be done. The results should always be supervised by someone in the hospital who has had at least a moderate amount of training in the procedure and who appreciates the responsibility involved." Numerous "blood banks" are being set up all over the country to

conserve blood for transfusion purposes. These banks have been eminently successful. Citrated blood may be kept for periods up to 2 weeks providing the ice box is kept at a low constant temperature of 39° to 41° F (4° to 5° C). Placental blood is an "inexhaustible" source of material for transfusion, according to J. R. Goodall, F. O. Andrews, G. T. Altimas and F. L. MacPhail¹²⁶. From the normal placenta, 100 to 150 cc. of polycythemic blood can be removed. This is sufficient for a "small" transfusion. B. C. Grodberg and E. L. Carey¹²⁷ cite their experiences with the use of placental blood in 75 cases. The necessity for carefully typing and cross-matching placental blood is stressed as the fetal blood differed from the maternal in 33 per cent of the cases. Minor reactions occurred in 5 per cent of the cases. H. Knoll and O. Schurek¹²⁸ recommend heparinizing the donor and thus dispensing with citrate. G. D. W. Murray and C. H. Best¹²⁹ recommend the use of *heparin* intravenously following operative procedures to diminish the possibility of postoperative thrombosis. Immunotransfusion is occasionally advocated. Thus M. Acuna and I. Fernandez¹³⁰ immunized donors with either stock or autogenous *vaccines*, and claimed definite reduction in mortality of severe sepsis, particularly that associated with pneumonia and bronchopneumonia, in 16 children.

Polycythemia—Polycythemia vera is probably unrecognized in many cases. It gives vague symptoms, which are often multiple.¹³¹ Vascular complications, particularly thrombosis, are common. In the series of 98 cases studied by I. L. Norman and E. V. Allen,¹³² about one-third had vascular conditions. If the many vascular diseases are viewed with the suspicion that polycythemia vera exists, it will be found in at least a small

percentage of cases. R. L. Haden¹³³ points out that the total red cell mass is greatly increased in the disease and that treatment should be directed against this feature. This is produced by *multiple venesections* for a period of 3 to 4 weeks, followed by the use of a *diet deficient in iron* (6 or less mg per diem).

Chronic Congestive Splenomegaly—L. J. Howells¹³⁴ reviews the results of treatment in 94 cases diagnosed as splenic anemia or Banti's syndrome, 51 were treated by splenectomy and 43 medically. The medical treatment was symptomatic. Splenectomy did not seem to improve the expectation of life or prevent the progress of cirrhosis of the liver or of the anemia or the occurrence of hematemesis. The final results, based on the progress of both hepatic disease and anemia in the 2 groups of patients, show that 22 of the 51 splenectomized patients and 20 of the 43 medically treated patients improved. There is thus no logical reason for retaining splenectomy as a routine. The treatment of hemorrhage due to esophageal varices is described by C. Henschen.¹³⁵ Splenectomy is not sufficient to prevent a fatal hemorrhage from various tributaries of the coronary gastric vein. The logical procedure, according to Henschen, is to *ligate all the venous channels* arising in the portal area and entering into the formation of the peri-esophageal and intraesophageal varices.

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DISEASES OF THE KIDNEY

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Introduction—During the past year the progress in the study of renal diseases has been manifested chiefly by investigations of the production of hypertension, the effect of feeding experiments upon the progress of the inflammatory lesions in the kidney and the effectiveness of proteins in stimulating the formation of plasma albumin and globulin. For the most part these reports have been of a research nature; yet their practical applicability is obvious. There have also been innumerable articles discussing various aspects of the etiology, clinical course and treatment of renal diseases, and while most of these reports do not present anything very new, in the aggregate they contain much valuable and practical information. Many of this year's articles emphasize the necessity of early recognition and treatment of the nephritides. The importance of the pathological physiology of the kidney is rapidly being more widely recognized than ever before. Piersol¹ has crystallized the trend of this type of thinking on the part of clinicians in a recent article on the value of the electrolyte, water and acid-base balance. He points out many of the important clinical investigations of the changes in electrolyte balance and shows the correlation to be looked for between functional impairment and structural changes in the kidney.

ACUTE NEPHRITIS

The classical textbook picture of acute nephritis is often lacking, and mild forms occur which are characterized by the urinary syndrome alone. This is especially common during the course of an acute upper respiratory infection or com-

mon cold. The urine, therefore, should be examined frequently during the course of any infection if mild forms are to be discovered. It is well known that infections such as tonsillitis, upper respiratory infections, sinusitis and scarlet fever are common forerunners of acute nephritis. However, rheumatic fever seems to be a more frequent cause than formerly supposed, according to a report by Salvesen.² In a series of 212 cases of rheumatic fever 10 cases of acute rheumatic nephritis were found.

Etiology and Pathogenesis—Baehr³ believes that acute glomerulonephritis is a sharply circumscribed entity with a specific etiology and pathogenesis. It is part of a disease of the body as a whole and its clinical manifestations are related to pathologic phenomena in various parts of the body. He disagrees with the conception of Bell that acute nephritis is an advanced stage of certain changes which are often found at death in various diseases. A positive diagnosis of acute glomerulonephritis, according to Baehr, can be made only if there are clinical evidences of vascular disturbances such as hypertension and edema in addition to urinary changes. This idea is at variance with many writers who contend that the diagnosis of acute glomerulonephritis should be made in the presence of urinary anomalies alone. He believes that "the sudden explosive occurrence of acute glomerulonephritis is a specific reaction concerned in some unknown manner with the mechanism of recovery from streptococcal infections."

In an attempt to decide the time relation of albuminuria and hypertension in postscarlatinal nephritis Carslaw⁴ in-

vestigated the blood pressure in a series of 50 cases of scarlet fever during the first three weeks of illness. A rise of pressure was noted in 27 patients during the second or third weeks, and 10 of these had albuminuria at the same period. In only 6 did the albuminuria follow the rise in pressure. Albuminuria occurred in 12 of the 23 that had no rise in pressure. The pressure rose in 17 of the 28 patients without albuminuria, that is, without apparent renal involvement. Of the 22 cases with albuminuria 16 were not preceded by a rise in systolic blood pressure. Clinical nephritis developed in 3 of the 59 patients and in only 1 of these cases was there a rise in blood pressure. He concludes that hypertension does not produce albuminuria nor does albuminuria mean that the blood pressure will be raised. Therefore, it is impossible to diagnose postscarlatinal nephritis by daily blood pressure.

Course and Prognosis—A series of 150 cases of acute nephritis was discussed by Murphy and Rastetter⁵ with special reference to the course and prognosis. They point out that more attention should be paid to the early recognition of acute nephritis and that one should not demand the full classical textbook picture before making a diagnosis. In their opinion, if milder forms of nephritis are recognized and treated, some patients will be saved from developing chronic nephritis. The fundamental principle in treatment is complete rest in bed until all evidence of kidney inflammation has disappeared. Removal of foci of infection and attention to certain dietary details are also emphasized.

Hypertension—Hypertension, according to Bell,⁶ may not be present during the entire course of acute glomerulonephritis and at times it is absent entirely. In mild cases the blood pres-

sure may be raised only during the first few days, and usually it returns to normal long before albumin disappears from the urine. Persistent hypertension indicates the development of chronic nephritis. In acute glomerulonephritis the flow of blood through the kidneys is reduced because of the widespread capillary destruction, and experimental evidence suggests that either this anemia of the kidney or the increased resistance in the renal circulation is in some way responsible for the hypertension. In some severe cases of acute glomerulonephritis, failure of the heart or vasomotor system to respond to the stimuli from the diseased kidney may account for the absence of hypertension.

Cardiac Involvement—Cardiac insufficiency may develop during the course of acute nephritis and there may be either frank heart failure or milder cardiac disturbances such as palpitation, tachycardia, pallor, enlargement or pulmonary congestion. Recently, Master, Jaffe and Dack⁷ found that cardiac insufficiency was common in a series of 24 cases and that at times it was severe enough to cause death.

Feller and Hurevitz⁸ studied 2 cases of acute nephritis with cardiac failure. In 1 case a biopsy of the deltoid muscle revealed a subacute perivascular inflammation involving particularly the arterioles. As the patient recovered, a second biopsy showed that the perivascular process was less severe and of a more chronic nature. In another case of acute nephritis a biopsy taken from the pectoralis major at the time of autopsy revealed an inflammatory lesion of the arterioles. This lesion was also found to be widespread and included the arterioles of the heart, but the glomerular damage was minimal. This has led the authors to conclude (a) that acute nephritis is part of a widespread

vascular disease which is occasionally severe enough to be called panarteriolitis and (b) that many patients who seem to have acute nephritis with cardiac failure actually have panarteriolitis with involvement of the vessels of the myocardium.

In a total of 55 patients with acute hemorrhagic nephritis Rubin and Rapoport⁹ observed 14 children with various degrees of cardiac involvement during the acute stage of their illness. The clinical evidences of cardiac involvement and failure which they observed were (a) Dyspnea, tachypnea and cough; (b) cardiac enlargement; (c) muffled heart tones; (d) rapid heart rate; (e) murmurs, usually a mitral systolic murmur which also is noted to be the last evidence of cardiac damage to disappear when recovery takes place; (f) engorgement of the veins, (g) gallop rhythm; (h) enlarged, tender liver; (i) pulmonary edema; (j) peripheral edema, and (k) electrocardiographic changes showing various degrees of myocardial damage. During the acute phase of the disease there are 2 factors which may affect the heart: Myocardial damage, and increased vascular peripheral resistance (hypertension). They cite the work of Longcope and his coworkers which showed that the hemolytic streptococcus is associated with acute hemorrhagic nephritis. Since myocardial damage is a fairly frequent complication of acute hemolytic streptococcal infection, it is possible that the same infection responsible for the acute nephritis also damages the heart. The second factor, hypertension, they believe, is immediately responsible for the impairment of cardiac function. Hypertension was present in all patients with acute hemorrhagic nephritis showing signs of cardiac insufficiency. In evaluating the reading of children's blood pressure it was noted

that the blood pressures which were not called abnormal at first were elevated in comparison to values obtained after the patient recovered. It was found that the elevation of the diastolic pressure is a more characteristic finding than elevation of systolic blood pressure. In the 14 patients reviewed, those who had the cardiac damage did not show a more severe nephritis than those with no cardiac involvement. The only deaths which occurred in the series of 55 nephritic patients were due to cardiac failure.

Garreton Silva, Hervé, Noguès and Forero¹⁰ made electrocardiographic studies of the heart in acute nephritis. The electrocardiogram was nearly always deformed and the modification of its complexes was strictly parallel to the severity of the cardiac symptoms. The most prominent alterations involved the interval between the S and T and the T wave, and there were no disturbances in the intracardiac conduction.

In discussing the course and outcome of acute hemorrhagic nephritis Longcope¹¹ divides the disease into 2 groups. The first group is always preceded by definite infection, usually caused by the hemolytic streptococcus. In this form the onset is characterized by the sudden appearance of 1 or all of 3 cardinal symptoms: Edema, abrupt rise in blood pressure, and the presence of red blood cells, casts and albumin in the urine. These symptoms, however, may be so mild and fleeting that they may escape attention or they may be very pronounced. There is no direct relationship between the severity of the primary attack of nephritis and the subsequent course. Death may occur during the acute attack usually from the infection itself or from a complicating pneumonia or from acute heart failure with edema of the lungs. In a few patients the disease advances to an active progressive stage resulting in

edema and termination in uremia at the end of a few weeks or months. Some of the patients pass on into the chronic stage, but the percentage of complete recovery is somewhere between 60 and 70 per cent. The second group of cases begins insidiously and is not usually preceded by an infection of which the patient is aware. Most of these patients first notice swelling of the feet and then gradual extension of the edema to the entire body. Definite infections were found in 13 of 25 patients in this group. The outcome of the disease in the second group of cases presents an entirely different picture. Only 1 of the 25 cases studied recovered, 5 were in a quiescent stage, in 7 the process had advanced to the stage of chronicity, 12, or almost 50 per cent, died. The prognosis for the first group is relatively good, but in the second group it is extremely grave. The relation between the 2 is not clear, but certain characteristic immunological reactions that are quite constant in the first group are found absent or suppressed in the second.

In any disease one wonders about the susceptibility of the individual to subsequent attacks. In acute nephritis the question arises as to whether the kidney is more vulnerable after healing to the streptococcal infection that caused the lesion. Loch, Lattle, Seegal and Jost,¹² after studying 10 patients with healed glomerulonephritis due to hemolytic streptococcus infection, found that in subsequent infections due to hemolytic streptococcus during the healed period there was no recurrence of nephritis.

Renal Disturbance Following Transfusions—The acute renal disturbance following blood transfusion is discussed by Baker,¹³ who reported a case in which urinary suppression followed transfusion with overheated blood. He describes the mechanism of post-

transfusion suppression in the light of older and recent work and concludes that the view put forward by Baker and Dodds in 1925 furnishes the only adequate explanation of the observed facts. According to them, urinary suppression results from an intrarenal obstruction due to excretion of hemoglobin with the urine of high acidity and salt concentration which causes the excreted hemoglobin to be converted into a granular deposit of hematin and to obstruct the renal tubules. Hemoglobin *per se* is innocuous to the kidney. Since precipitates of hematin are more soluble in alkaline than in acid urine, alkalinization should help in dissolving some of the precipitate in the tubules unless there is complete suppression. Early recognition and prompt treatment by alkalinization appear to offer the best prospect of recovery.

Similar observations by DeGowin Warner and Randall¹⁴ have shown that when a dog is transfused with canine blood, death may result from renal insufficiency if the urine is acid. This does not occur when the urine is alkaline at the time of transfusion. The anatomical picture of obstruction of the renal tubules by hemoglobin pigment is sufficient to be the chief cause of the renal insufficiency in the dogs observed. In addition a nephrotoxic process often operates and may cause renal insufficiency independently. In studying 9 human beings who died of renal insufficiency after hemolysis, they found that precipitation of the hemoglobin pigment in the tubular lumens had occurred to a slight degree at least. However, in most of the cases not enough tubules were obstructed to produce any important diminution in renal function. The presence of pigment casts and of hemosiderosis is important in making the diagnosis of transfusion nephropathy.

The predominant lesions are more often degenerative changes in the tubules and interstitial edema.

In another article DeGowin¹⁵ cites studies made on the reaction of 3500 blood transfusions. Citrated blood was used almost exclusively. There were 7 deaths in the entire series (1.2 per cent); 5 persons died of renal insufficiency and 2 of pulmonary edema. Reference is made to the article of DeGowin, Osterhagen and Andersch,¹⁶ in which it was shown that in dogs alkalinization of the urine will protect the kidneys from the excreted hemoglobin if hemolysis occurs. They believe, therefore, that alkalinization of the urine of the recipient before transfusion is a desirable measure. As an additional precaution blood should be typed, using typing sera of high titer, and the transfusion should be discontinued immediately on the occurrence of any unusual symptom.

Treatment of Acute Nephritis—

According to Holten,¹⁷ *rest in bed* is the best means of avoiding chronic nephritis, the greatest danger that threatens the patient with acute nephritis. He advocates keeping the patient in bed until microscopic examination shows the urine to be without erythrocytes. Recovery is possible even if the erythrocytes persist in the urine for more than 3 months as long as the sedimentation and function tests disclose a tendency to improvement. In his opinion there is sure occurrence of recovery in about 75 per cent of the cases of acute nephritis.

In the treatment of acute nephritis Longcope¹¹ believes that elimination or cure of the infection seems to be of prime importance in hastening convalescence and effecting recovery. With this in mind *tonsillectomy*, *surgical drainage of sinus infection* and *radiotherapy* have been employed. Recently *sulfanilamide* has been used in treating

acute nephritis. Marshall, in his pharmacological experiments, found that even large doses produced no demonstrable injurious effects on the kidneys of normal animals. The results so far have been encouraging enough to warrant further use of the drug in patients shown to have active infection due to hemolytic streptococci.

Chapman¹⁸ reports a case of post-scarlatinal nephritis accompanied by streptococcic bacteremia. Ten cubic centimeters of *prontosil* were given intramuscularly every 4 hours for 6 doses followed by *prontylin*, 5 grains, every 4 hours for 2 weeks. After 4 days of treatment the temperature rose to 100° F only once, ranging between 96.8° F and 100° F. per rectum for the remaining period. The patient became completely well and a check-up 11½ months later revealed no evidence of illness.

Concerning the treatment of acute nephritis Rubin and Rapoport⁹ state that if the heart seems normal, if there is no elevation of the blood pressure and if the major disorder is the disturbance of toxic metabolites, therapy might include *forcing of fluids*. When acidosis appears they recommend the administration of alkali such as *sodium lactate*. In 1 of their cases in which *anuria* was present, *fluids* were given in large amounts, and despite the increase of edema the intoxication was lessened. After 5 days the anuria disappeared and diuresis was established. If hypertension is present in the course of acute nephritis, its control is important. Fluids should be restricted as a further adjunct in the treatment of hypertension with myocardial damage. They also recommend the *intramuscular injection* of 50 per cent *magnesium sulfate* in a dosage of 0.2 cc per kg. of body weight. Since the studies of Pickering¹⁹ showed convincing evidence that the hyperten-

sion in acute nephritis is due to vasospasm, experimental work has been done which shows that magnesium relieves hypertension in rats produced by ergotamine tartrate which causes a vasospasm. It was observed that magnesium carbonate added to the diet of rats prevented hypertension if given before the administration of ergotamine tartrate, and when given to animals after hypertension had been produced the blood pressure returned to normal. In a 7-year-old boy with acute hemorrhagic nephritis and hypertension additional observations were made concerning the action of magnesium in reducing hypertension. The patient was put on a constant intake of fluid (30 cc) per hour and an hourly determination of the output of urine was estimated. Ninety cubic centimeters of a 50 per cent solution of sucrose were given intravenously. This was followed by marked diuresis but no drop in blood pressure. Fourteen hours later a 50 per cent solution of magnesium sulfate was given intramuscularly (0.2 cc per kg of body weight). Following this there was a prompt drop in both the systolic and diastolic blood pressures with no diuresis. Rubin and Rapoport also found beneficial effects of intramuscular injection of magnesium sulfate in patients with hypertensive encephalopathy, and although these effects have been ascribed to dehydration, clinical experiments indicate that the improvement is due to the relief of vasospasm. The effect of a single dose of magnesium sulfate is usually prompt, and the systolic and diastolic pressures are lowered within an hour and tend to remain so for several hours. The first dose can be repeated at 4-hour intervals. One caution must be observed, and that is in cases with marked impairment of renal function and low urinary output and in which there is retention of metabolites an accumulation of mag-

nesium might occur with a resultant narcotic effect. The authors did not encounter this ill effect. Additional measures which are recommended in the treatment of cardiac damage are *digitalis, oxygen, sedation* and possible *phlebotomy* if advanced cardiac failure is present.

An interesting observation has been made by Bliss²⁰ concerning the severe ulceration of the cheeks and tongue in acute nephritis. The cause is ascribed to the action of the tartar of the teeth on the saliva. The tartar which he found to contain urease, when scraped from the teeth of normal and nephritic dogs, hydrolyzes urea to ammonia in a few minutes just as urease does. It was further demonstrated that ammonia actually does damage such tissues. The tartar should be removed to relieve or prevent this condition.

CHRONIC NEPHRITIS

The main stumbling block in the diagnosis and treatment of renal diseases, especially the chronic forms, is that the signs and symptoms remain for the most part below the threshold of clinical recognition until the disease has produced irreparable damage to the kidney. Nephritis is like an iceberg floating in the sea whose visible ninth appears benign, but whose submerged eight-ninths is a menace. Patients with the milder symptoms, such as slight albuminuria and a few casts, red blood cells and pus cells in the urine, are frequently neglected until hypertension, edema or nitrogen retention appear. Then treatment is far less effective than it would have been at an earlier stage of the disease.

The protean character of the signs and symptoms of terminal hemorrhagic nephritis are outlined by Page.²¹ The following points are especially well exempli-

fied in the case he describes: (a) An insidious onset means a fatal outcome. (b) The terminal stage may last for months. (c) Poor nutrition contributes to discomfort and ill health; therefore, sufficient protein should be given. (d) Salt restriction may relieve edema even though plasma proteins do not rise above the critical level. If polyuria does not occur, salt restriction may be extreme without producing hypochloremia (e) Even when hemoglobin is not greatly reduced, death may occur in uremia. Iron will not help the condition. (f) Arterial blood pressure may alternate between a high level and normal (g) Eyeground changes may not be present until weeks or days before death. (h) Oliguria may last for as long as 18 days without producing marked symptoms (i) Increased cells may be found in the pituitary gland.

The protein in the diet has often been considered injurious to the kidney especially if it is diseased. Chronic nephritis has been produced in rats by feeding them diets high in protein. These experiments, conducted by Blatherwick and Medlar,²² show that functional impairment of the kidney may exist for some time before histological changes indicative of nephritis become apparent. Albumin or casts in the urine were interpreted as indicative of functional impairment of the kidney although they are not necessarily proof of nephritis. When irreparable damage occurred, retention of nonprotein nitrogen, inversion of the albumin-globulin ratio and hypercholesterolemia were observed. The injurious factor may exist as such in the diet or may be produced during metabolism. If harmful substances exist in the diet they may not necessarily be confined to the protein fraction. Nephritis may be introduced by an abnormal excretion of normal end products, by an

excretion of abnormal products, or by the retention of certain substances.

One of the most suggestive recent investigations of the effect of dietary protein is the work of Farr and Smadel,²³ who produced nephritis in rats by the injection of nephrotoxic serum. If the rat diet contained only 5 per cent of protein, acute nephritis healed readily and completely. The rats whose diet contained 40 per cent of protein developed progressive nephritis and died at an average of 6 months after injection of the serum.

Conversely, Campbell,²⁴ in studying the effect of high protein diets on the kidneys of rats, found that when feeding a diet containing 33 per cent of the total fuel value as protein calories, there were no evidences of kidney damage. The rat was chosen for the experiment because of the similarity between the metabolism of the rat and the human. The diet of most American people contains approximately 10 per cent of the total energy value as protein calories. From this work it might be concluded that the protein in the average daily American diet probably has no injurious effect on normal kidneys.

Clinically it has been shown that symptomatic improvement does occur in some cases of chronic nephritis when a higher protein diet is given. Mosenthal²⁵ points out the disastrous influence of low protein diets in bringing about edema and anemia in chronic nephritis, and the remedial and preventive effect of a liberal intake in forestalling and relieving these conditions. He cites a case of a patient who developed edema and anemia while on a low protein diet. When the protein was increased the edema and anemia disappeared, the blood pressure was lowered and there was a distinct improvement in impaired vision incidental to the retinitis. He states that a

high protein diet may be of help in controlling hypertension and in relieving retinitis

The maintenance of a satisfactory mineral balance is of considerable importance because of its close relation to nephritic edema, uremia and acidosis. Recently the work of Barker and Robinson²⁶ has brought out several valuable facts in this connection. Patients with long standing chronic renal disease were placed on a diet kept constant in nitrogen, phosphorus, sulfur, chloride, sodium and potassium. In addition sodium chloride, potassium chloride, sodium citrate, sodium bicarbonate, potassium citrate, calcium gluconate, calcium chloride, phosphoric acid, ammonium sulfate or combinations of these drugs were given in calculated amounts. When sodium was added to the basic diet it was observed that there was storage of fluid, elevation of blood pressure and decrease in urea clearance. Chlorides given, as ammonium or calcium chloride frequently decreased the edema but the associated acidosis aggravated the symptoms and depressed renal function. Potassium chloride, however, usually effected a moderate or complete loss of edema with an occasional improvement of urea clearance. When phosphate and sulfate ions were given they were found to be effective occasionally in clearing the edema and reducing blood pressure. The phosphate ions, given as phosphoric acid, tended to cause acidosis and increase renal irritation. The sulfate ions in the form of ammonium sulfate proved more satisfactory and caused a fall in blood pressure, disappearance of edema and improvement in urea clearance. An alleviation of subjective symptoms was also noted. The conclusion is drawn that when a patient is placed on a low protein diet the phosphate ions of the

meat are given up with a resultant aggravation of symptoms.

Renal Function Tests—In diseases of many internal organs, such as the liver, heart and lungs, reserve capacity is so great that functional failure occurs only when the organ is diseased beyond repair. This fortunately is not true of the kidney, for here the renal function tests indicate milder degrees of insufficiency at a time when prompt and adequate treatment may be effective in protecting the patient from complete renal insufficiency.

In determining whether the renal lesion in acute nephritis persists or has healed, Murphy^{5, 27} states that no 1 test is reliable as a guide, but that a composite picture furnished by several tests may be a fairly accurate prognostic index. He points out that (a) The presence of hypertension indicates an active glomerular lesion. (b) albuminuria decreases when healing has taken place, (c) the dilution concentration test of Vollhard is a reliable indication of the progression of the kidney lesion, (d) the blood urea clearance test is considered the most satisfactory but in most cases it has no advantage over the dilution concentration test, (e) the determination of the sedimentation rate of the erythrocytes is of distinct aid in prognosis. When the renal lesion is becoming quiescent the rate falls and when the lesion is progressing it rises.

Wilson,²⁸ in discussing the clinical application of renal efficiency tests, states that the ability of the kidney to concentrate and dilute urine and the urea clearance test are valuable aids in evaluating renal function. The estimation of the urea, nonprotein nitrogen and other elements of the blood is valuable only if these are elevated, but normal figures give little information as to the degree of renal reserve. The chemical constituents may also be elevated by extrarenal factors

causing the so-called extrarenal azotemia. Low values of the dye excretion tests, such as the phenolsulfonphthalein test, do not necessarily indicate renal damage, but may mean that there is circulatory failure.

According to Stieglitz,²⁹ it is impossible to judge the severity of renal injury by the intensity or duration of such common symptoms as albuminuria, edema, casts, and arterial hypertension alone. Many of these phenomena, especially edema and hypertension, may be due largely to extrarenal factors. Diagnosis should include quantitative as well as qualitative impressions, therefore functional studies are necessary. Before kidney breakdown occurs, there is usually a long period of impaired reserve which may be detected by renal function studies. We start life with a renal margin of safety of about 400 per cent, but inevitably the transient infections and insults from the vicissitudes of existence lower this margin. The depletion is tremendously accelerated by actual renal disease. The concentration test is thus far the most sensitive measure of functional reserve. The urea clearance is more accurate in advanced nephritis, and phenol-sulfonphthalein excretion is grossly impaired only when damage is extensive. The glomerular function test with sodium ferrocyanide is still experimental.

Winkler and Parra³⁰ studied the manner of variation of creatinine, sucrose and urea clearances in a group of subjects with renal disease and found that the absolute magnitude of all 3 is usually consistently and uniformly reduced, while their normal order, creatinine greater than sucrose and sucrose greater than urea, is generally maintained. In "nephrosis" all the clearances may be normal. The behavior of these clearances in the presence of renal disease is consistent with the theory that they all are relative measures

of filtration and that the degree of reduction reflects quantitatively the degree of reduction of the glomerular filtration rate.

An attempt to differentiate Bright's disease from specific toxemia of pregnancy by means of renal function tests was made by Chesley.³¹ He concluded that the urea nitrogen/nonprotein nitrogen and 2-hour fractional phenolsulfonphthalein excretion tests are apparently not very sensitive and are influenced by extrarenal factors. The specific gravity test is most sensitive. The urea clearance test is the most generally applicable of all. He showed that the normal value for the urea clearance is the same in normal pregnancy as it is out of pregnancy, and also that in eclampsia, pre-eclampsia and hypertension the urea clearance does not differ significantly from values observed in normal patients. However, in Bright's disease complicated by pregnancy the clearance is often less than 70 per cent. He thus concludes that the urea clearance test will serve to differentiate renal disease of measurable degree from specific toxemia of pregnancy.

Treatment of Chronic Nephritis—In discussing the clinical aspects of nephritis, Loeb³² states that in the treatment of chronic nephritis the dietetic regime involves the questions of protein, salt and fluid. He believes that a patient with chronic nephritis with edema or advanced renal insufficiency should not be placed on a regulated amount of protein and that the diet should be governed by the adage of "moderation in all things." However, when *nitrogen retention is present*, **protein** should be **restricted** to 40 to 50 Gm a day. If anorexia and loss of weight and strength result, the patient should be allowed to make his own diet. *When edema occurs* with low serum protein, Loeb employs a **high protein diet**, although he points out that there is almost always disappoint-

ment in its effect on the serum protein. In the presence of edema, 100 to 200 Gm. of protein a day are recommended, and in addition **salt** should be **restricted**. However, too great limitation of salt may result in anorexia, nausea and vomiting. When edema is absent there is no sound basis for salt restriction. He believes that there should be limitation of fluid intake in the presence of edema, but only in accordance with the degree of retention and in the presence of cardiac insufficiency. As the renal insufficiency advances, the fluid intake should be increased to compensate for the loss in concentration power. He emphasizes the fact that the patient should be protected from recurrent or persistent infection of the upper respiratory tract and that **tonsillectomy** should be performed routinely in all patients with nephritis.

In chronic nephritis with edema and little or no nitrogen retention, Bannick³³ believes that the diet should contain ample protein to insure a positive nitrogen balance and an additional supply for storage. About 100 Gm. daily is adequate for an adult. Salt is rigidly restricted and fluid is given in moderate amounts. **Diuretics** are indicated, and both the acid and alkali variety have shown good results. If salyrgan is used, it should be given cautiously. **Digitalis** is beneficial if there is evidence of myocardial failure. Some physicians have obtained good results with **acacia**. All definite **foci of infection** should be **removed** and a warm dry climate is preferable. If both edema and nitrogen retention are present, a salt-free diet with moderate protein reduction (50 to 60 Gm. daily) is best, but a positive nitrogen balance should be maintained. A **liberal fluid intake** (some intravenously) is given until azotemia is controlled. Suitable diuretics, such as **potassium citrate**, or **potassium bicarbonate** may be used cau-

tiously, and **blood transfusion** is sometimes beneficial. When there is nitrogen retention without edema, proteins are restricted, and a liberal fluid intake (2500 to 3000 cc. daily) is allowed by mouth unless nausea or vomiting make other routes advisable. Diuretics do no good except for digitalis which is indicated when cardiac decompensation is present. Blood transfusion may help temporarily, but the anemia is very resistant to treatment. Since heart failure is always threatening, the cardiac load should be reduced as much as possible.

In an article on the treatment of advanced nephritis, Plotz, Howard and Marzullo³⁴ state that patients in the later stages of nephritis present a hopeless problem as far as cure is concerned, but their comfort and length of life may be greatly influenced by treatment. Frank infections should be treated, avoiding operative measures if possible. **Arterial hypertension** is best treated by **bed rest**, **simple sedatives**, **magnesium sulfate** intravenously and by mouth and **venesection**. The diet must be individualized and **adequate vitamin intake** is necessary. A mixed diet is best as long as the patient can tolerate it. When anorexia and renal failure set in, however, this must be modified and **milk** should form the basis of the diet. **Glucose** may be given parenterally. **Rest** should be sufficient, **exercise restricted** and attention given to the skin and bowels.

For the treatment of **hypertensive encephalopathy**, **venesection** is probably the most effective measure. **Spinal puncture**, intravenous or intramuscular **magnesium sulfate**, **chloral hydrate** by rectum, **hypertonic solutions**, and in extreme cases **chloroform** are also helpful.

Lyon³⁵ points out the beneficial action of the basic ash régime in chronic nephritis. Since animal protein is a rich

source of acid radicles it is kept at a minimum. Lyon's diet consists mainly of milk and vegetables and fruits which are mostly basic in character. He found that the pH of the urine on the basic ash diet ranged about 6.6 while on the acid ash diet it was lower—about 5.8. He concluded that patients with chronic nephritis progressed much more satisfactorily on a diet that was limited in meat, bread, eggs and rice

In the treatment of *acidosis* in renal insufficiency Deakin³⁶ advises the use of **sodium r-lactate** by mouth or the intravenous administration of a sixth molar sodium r-lactate solution. He cites several cases in which the patients were in impending coma and were clinically improved after the administration of sodium r-lactate. In all of the cases there was an elevated nonprotein nitrogen and a low carbon dioxide combining power both of which returned toward normal after the administration of sodium r-lactate.

Diuresis—A summary of our present knowledge of the subject of diuresis is clearly and completely given by Christian.³⁷ He points out that the treatment of renal edema is just the same whether we are dealing with nephrosis, chronic nephritis, or acute nephritis. **Mercurial diuretics** are more effective than those of the xanthine group and as a rule cause no renal irritation. **Urea** in large doses is an efficient diuretic if it can be tolerated by the patient. **Salyrgan** and **mercupurin** have been made available as suppositories, and in a more recent article Christian³⁸ states that these are very effective in both renal and cardiac edema.

In an article on the use of diuretics in Bright's disease MacDonald³⁹ points out that in hemorrhagic Bright's disease diuretics should not be used. In the active chronic stage the use of **digitalis** is ad-

vised if myocardial insufficiency is present. He believes that the mercurials are of some value in reducing edema, but care should be used to see that the albuminuria and hematuria are not increased by its use and that no mercurialism develops from retention because of reduced renal function. In degenerative Bright's disease where the only pathology is an involvement of the tubules, the potassium salts, especially **potassium nitrate**, are useful. In this condition the intravenous administration of a **hypertonic solution of sugar** is, in addition to the diuretic effect which is frequently obtained, valuable as a source of energy. The mercurial diuretics such as **novasurol** and **salyrgan** can also be used in this degenerative form of the disease without danger in their administration. In some cases, particularly those associated with a disturbance of calcium metabolism and clinical evidence of tetany the use of **parathyroid extract** has given good diuretic response. In renal lesions of vascular origin where edema is more frequently of cardiac than of renal origin digitalis, intravenous sugar solutions and salyrgan either alone or combined with **ammonium nitrate** are of distinct value.

NEPHROSIS

The chief difficulty in the recognition of chronic (lipoid) nephrosis is the fact that many patients with chronic glomerulonephritis present an almost identical picture. Histologically, however, the difference is easily apparent even though there may be minimal glomerular involvement. If, in chronic nephritis, there is extensive tubular degeneration with scant glomerular disease, the nephrotic syndrome is likely to be the most prominent clinically; on the other hand, if the glomerular lesions predominate the classical picture of glomerulonephritis pre-

vails. There may be a mixture of the 2 and sometimes the nephrotic changes so dominate the picture that the diagnosis of lipoid nephrosis is erroneously made. The fact that the patient with nephrosis gets well and that certain features necessary for a diagnosis of chronic glomerulonephritis are absent places it in a category apart from other forms of Bright's disease.

According to Epstein⁴⁰ the term nephrosis as now generally applied represents a compromise between pathologists and clinicians. From the pathological standpoint it includes all forms of renal disease with tubular degeneration while according to the clinical concept it refers to a group of diseases with edema, oliguria, albuminuria and characteristic biochemical changes in the blood. The pathological prototype of nephrosis is the degenerative process of the kidney tubules which results from certain metallic poisons and bacterial toxins.

Clinical Course- The clinical course is specific and differs widely from that manifested by the group of cases generally designated as chronic nephritis. Chronic nephrosis in its purest form is a disease which begins insidiously, is of unknown origin, and runs a long course characterized by albuminuria, oliguria, and edema without circulatory changes or impairment of renal function but with certain distinctive changes in the blood. The question is raised whether genuine chronic nephrosis is a renal or a metabolic disorder.

Etiology-The etiology of true nephrosis is not known and while the albuminuria is of necessity a renal phenomenon, it is not always a proof of the existence of renal disease. Some evidence suggests a metabolic derangement as the pathogenic factor. In the opinion of most pathologists the kidneys in genuine nephrosis show tubular degeneration

and lipoid infiltration but no evidence of inflammation. However, other pathologists claim that it is a degenerative type of nephritis in which the inflammatory processes subside and degenerative tubular lesions persist.

Among recent articles on lipemic nephrosis, one by Fahr⁴¹ deserves consideration. He believes that all the symptoms can easily be explained on the well-founded assumption that the ultrafilter of the glomerulus, which has been shown in most cases to be altered morphologically by the newer staining methods, has become hyperpermeable. Therefore, the serum albumin from the blood filters off into the urine day by day. This reduces the content of the serum albumin in the blood until the colloid osmotic pressure is lowered to about one-half. When it is reduced to this critical level much of the ingested water and salt are filtered off into the skin and other tissues causing edema. The lowered basal metabolic rate in patients with chronic nephrosis is due to the fact that the food intake is usually small and the height-weight formula, due to the water in the tissues, lowers the basal rate. The circulating thyroid hormone may be removed from the blood stream along with the serum proteins. It is Fahr's opinion that chronic genuine or lipemic nephrosis is a disease of the glomerulus of the kidney and that there is no marked change in tubular function. Two cases, fully studied, lead to the conclusion that the real and essential pathologic process in chronic lipemic or genuine nephrosis is the thickening and increased permeability of the basement membrane, and that lipemic nephrosis is only part of the picture of glomerulonephritis.

Murphy, Warfield, Grill and Annis⁴² present a review of 9 cases of genuine lipoid nephrosis studied over a variable period of time. One patient was observed

for 15 years, 2 for 12 years, 1 for 7 years, 1 for 5 years, 2 for 2 years and 1 for 3 months. Two of the patients died and were studied post mortem; 6 recovered completely, and 1 is under observation. One of the patients studied post mortem showed no evidence of structural change in the glomeruli and this fact was confirmed by Dr Bell. One of the main reasons for making this distinction between lipoid nephrosis and chronic glomerulonephritis is that patients with lipoid nephrosis recover while the others usually do not. The disease is identified clinically by certain positive manifestations and by the absence of certain other features found in chronic glomerulonephritis. The positive features are marked albuminuria, hypercholesterolemia, edema and doubly refractive lipoids in the urine. Hypertension, nitrogen retention, genuine uremia and an abnormal number of red blood cells in the urinary sediment are lacking. There are no indications of cardiovascular changes such as hypertrophy, arteriosclerosis or albuminuric retinitis. The plasma protein, particularly the plasma albumin, is markedly reduced.

Since the edema of nephrosis is associated with a low plasma protein, studies on the effect of feeding high protein diets to nephrotic patients have been made periodically. Most recently Melnick and Cowgill⁴³ have given a complete review of the problem of the loss and lack theory in relation to proteinemia and edema. They support the belief that the loss and lack theory does not account for the abnormally low plasma protein in these cases, but that some other factor such as the protein forming mechanism of the body is involved. This mechanism can be stimulated to some degree by a high protein diet.

In studying the assimilation of protein in young children with the nephrotic syndrome, Farr⁴⁴ found that the maximum nitrogen retention occurred when the dietary protein intake was about 3.2 Gm. per kg. of ideal body weight. Feeding more protein resulted in less retention. The protein intake producing maximum assimilation in nephrotic children was similar to that found by other observers to be optimal for growth in normal children.

A metabolic study of 5 children with the nephrotic syndrome was made by Mitchell, *et al.*⁴⁵ In their report they present the clinical data, the effect of various treatments, records of excretion of urinary protein, results of basal metabolism tests, and studies of the blood and energy exchange. They found that no prolonged general improvement was accomplished with any procedure. The result of their investigation showed that the basal metabolism of all patients was within normal limits according to the standards of Benedict and Talbot and with 1 exception to the standard of Harris and Benedict. They concluded that the energy exchange of a nephrotic patient is normal.

Treatment—Favorable results in the treatment of nephrosis with *human serum* were reported by Aldrich, Stokes, Killingsworth and McGunness.⁴⁶ The serum was developed by the lyophilic process brought out by Florsdorf and Mudd in 1934 which makes a dry, porous powder that may be dissolved in one-fourth its original volume of water or serum. Eighty cubic centimeters of this concentrated human serum were used. This is equivalent to approximately 320 cc. of normal solution. Immediate diuresis took place in 6 of the 9 patients in which this treatment was instituted. In 4 of the patients who lost their edema urinary abnormalities also disappeared.

within a few weeks. It is believed that injection of this serum may have initiated some unknown physiological response and perhaps caused a spontaneous renal crisis. The rise in serum protein level was not significant enough to account for the diuresis and the disappearance of edema.

Schlutz and Collier¹⁷ recommended heroic doses of *alkali* in the treatment of nephrosis. They refer to an article by Osman who advocated the treatment of the acute and chronic forms of nephritis with high doses of alkali, the result being especially beneficial in cases in which generalized anasarca and ascites were the predominant features. The basis for this form of treatment lies in the theory that the colloidal proteins of the body tissue and cells have the property of imbibing or parting with water with alterations in the surrounding medium. Any change in the acid-base relationship results in significant change in cellular water content and its distribution in the body. The effect of this form of treatment is most favorable in cases presenting edema, albuminuria and low urinary output. It is least effective in the chronic interstitial forms with hypertension. The use of large doses of alkali is not without danger, and overdosage must be guarded against by checking the plasma bicarbonate. An ordinary *mixed diet* without restriction of protein or salt can be allowed and there need be no excessive restriction of fluid except that the intake should not greatly exceed the output. The alkali is given in the form of *potassium citrate* and *bicarbonate* and *sodium citrate* and *bicarbonate* in equal quantities. In children the initial dose is from 2 to 3 Gm. 3 times a day. The dose is increased by several grams a day until the pH of the urine is from 7 to 7.6. Doses of from 30 to 40 Gm a day or even more may be given. At

first the edema increases, but, in spite of this, alkalization is continued. After the height of the dose has been reached, marked diuresis sets in. Alkalization should be continued until the edema has disappeared. The authors point out that 3 dangerous symptoms must be looked for: (a) Tetany and convulsions which can be controlled by intramuscular injection of 0.05 Gm of *calcium chloride*; (b) signs of dangerous heart weakness, and (c) diarrhea. When there is heart weakness and excessive diarrhea, the dose of alkali, particularly the potassium salts, must be reduced. It is seldom necessary to reduce the dose more than one-third of the maximum amount. The series reported comprised 7 cases, 3 of which recovered completely; 4 cases were fatal. In 2 of the cases, autopsy revealed extensive renal damage, showing that the patients did not have true nephrosis. Pneumococcic peritonitis caused death in 2 cases before the high alkali treatment was well started and a third child died of heart failure before alkaline therapy was begun. The fourth patient had true nephrosis and responded well to treatment but succumbed to streptococcic infection with pneumonia and peritonitis.

To eliminate the edema when the nephrotic syndrome is present, Sheldburne¹⁸ enthusiastically advises the use of *acacia*. He points out that the high protein diet alone will rarely raise the level of the plasma proteins fast enough to eliminate the edema. However, by using the high protein diet and acacia, he believes that one can remove edema in a few days. When the edema in chronic nephritis is due to cardiac failure or capillary damage the use of acacia is not worth while. Likewise in the edema of acute nephritis which is associated with damaged capillaries, acacia is not indicated.

Landis⁴⁹ also studied the effect of acacia therapy in 6 cases of nephrosis and found that its administration did not affect hematuria, cylindruria or albuminuria significantly. By using repeated daily doses of not more than 30 Gm., the total dosage being 180 Gm. or less, with the combination of a low fluid intake and rigid salt restriction, it was found that acacia produced a satisfactory diuresis in 5 of the 6 patients. In 1 patient acacia in itself did not produce diuresis, but it apparently increased the effectiveness of *theophyllin* with *ethylenediamine* as a diuretic.

The fact that improvement followed intercurrent febrile disease in 39 cases of lipoid nephrosis was noted by Clément.⁵⁰ The appearance of fever was often accompanied by an increase in albuminuria at the onset, but was followed by diureses, decreasing albuminuria and disappearance of the edema and effusion. In addition the general condition of the patient seemed to improve. He cites a case in which fever induced with typhoid vaccine at intervals of 6 to 10 days was followed by a clinical cure which has lasted for 18 months.

ESSENTIAL HYPERTENSION (THE NEPHROSCLEROSES)

The chief interest in the subject of hypertension continues to center around the work of Goldblatt⁵¹ and his associates who have produced hypertension in animals by means of renal ischemia caused by the application of clamps to the renal arteries. This work has been amply corroborated by many workers and now there seems to be no doubt that, in animals at least, renal ischemia produces permanent hypertension. The interesting problem of the surgical treatment of hypertension has been interwoven with the research work. Allen and

Adson⁵² believe that results of operation for essential hypertension can be predicted if the response of the blood pressure to rest, sleep, sedatives and intravenous pentothal sodium is known. These authors state that about 70 per cent of their patients were benefited clinically by operative procedure. Their operation consists of bilateral subdiaphragmatic extraperitoneal resection of the splanchnic nerves, celiac ganglions and upper lumbar sympathetic ganglions.

Crile⁵³ reports favorable results from a different sort of operation. He drew his conclusions from the effects of *celiac ganglionectomy* on 129 patients with essential hypertension.

The results of *subdiaphragmatic extensive sympathectomy* in a large series of cases studied by Craig⁵⁴ were satisfactory. Cases were selected by means of 4 tests, (a) 24 consecutive hourly determinations of blood pressure were made while the patient was in bed to establish the maximum, minimum and average blood pressures, (b) slow and intermittent intravenous injection of 5 per cent solution of *pentothal sodium* was made until there was no further drop in blood pressure, (c) $\frac{1}{2}$ grain of *sodium nitrite* was administered at intervals of 30 minutes until 6 doses had been given, (d) hourly determinations of blood pressure were made during rest and sleep for a minimum of 24 hours. If the pressure dropped nearly to normal and if the patient was under 50 years of age the operation was considered. Contraindications for operation are (a) an age of more than 50 years, (b) congestive heart failure, (c) angina pectoris, (d) marked renal insufficiency, and (e) advanced arteriosclerosis.

It is pointed out by Page⁵⁵ that *resection* of the *splanchnic nerves* produced many of the same effects that are observed after section of the anterior

roots, but that the benefits are often more transient. In most of his patients with essential hypertension a definite upward trend in the blood pressure was observed 2 years or more after operation, but in others lower levels have persisted. However, in no case has the blood pressure fallen to and remained at normal. Of 8 patients with malignant hypertension subjected to section of the anterior spinal nerve roots, 4 showed no significant change in blood pressure while in 4 others definitely lower levels were established. He believes that medical measures, such as sodium thiocyanate and rest in bed, have not given as satisfactory symptomatic relief as surgical procedures.

After evaluating the surgical treatment of hypertension Heuer⁷⁶ concluded that therapeutic attacks directed at certain glands of internal secretion, such as subtotal adrenalectomy, will not solve the problem of the treatment of hypertension. In considering splanchnic nerve resection he feels that higher splanchnic vessels contribute an important flexible reservoir which governs the level of arterial pressure, and that there is also a peripheral motor mechanism residing in the blood vessels themselves which may sustain the blood pressure. However, his studies on the effect of anterior nerve section show that in early mild hypertension there is no apparent tendency of the blood pressure to rise and again approach the preoperative level even after 2 to 3 years. With few exceptions anterior nerve root resection has caused a striking improvement in headaches and other subjective symptoms, an improvement satisfactory enough to justify operation on this basis alone. There is also a striking disappearance of papilledema, hemorrhage and exudates in the eyegrounds. The possibilities of surgery in the treatment of hypertension should be further

explored, but encouraging results have been experienced.

Allen and Adson⁷⁷ discussed extensive sympathectomy for essential hypertension and reported the following results in its effect on the blood pressure: (a) Failure in 20 per cent of the cases, (b) temporary relief in 28 per cent of the cases, (c) good results in 24 per cent. However, there is clinical improvement in a large percentage of cases regardless of the effects on the blood pressure. They have concluded that it is advisable to operate on more patients with mild hypertension and fewer patients with severe hypertension.

In spite of these favorable reports general opinion among internists continues to be that surgical procedures are major operations which should be reserved for comparatively few patients who are very likely to be benefited by these radical procedures. Most patients with hypertension can be treated adequately without resorting to such extensive operative procedures.

Hypertension is divided into 3 forms by Mosenthal,⁷⁸ hypertension accompanying albuminuria, hypertension as a sequel to renal dysfunction, and idiopathic (essential) hypertension. In discussing the first type he stated that in cases which begin with albuminuria the hypertension frequently becomes the dominant complication and outstrips renal insufficiency, anemia or uremia as a cause of death. When hypertension is a sequel to renal dysfunction, the rise in blood pressure is a direct result of inadequate renal function and in those cases of kidney deficiency in which hypertension is absent this lack is attributed to a constitutional weakness which lessens the power of the cardiac and arterial muscles. Essential hypertension is defined as a functional disorder characterized by progressive rise of both sys-

tolic and diastolic arterial pressures. The capillary pressure is normal in hypertensive subjects, showing that the peripheral resistance is adjusted so that a normal capillary circulation is maintained. The generally accepted view is that a generalized contraction of the arterioles causes hypertension. However, it is an established fact that arterioles dilate or contract in response to a drop or increase in blood pressure. Mosenthal concludes, therefore, that increased arteriolar or peripheral resistance is a compensatory phenomenon for a hypertension produced by other agencies, presumably augmented tonicity of the muscular arteries. He believes that the term malignant hypertension should be abandoned and that it would serve a better purpose to classify essential hypertension as mild or severe, the severe type including cases with a diastolic pressure constantly above 140 which constitutes a menace through various vascular complications.

In pointing out the difference between malignant and benign hypertension, Ellis⁵⁹ stresses the importance of the presence or absence of papilledema. This is the most important sign of malignant hypertension and is invariably present when symptoms first appear. If papilledema is absent a diagnosis of benign hypertension must be made even in the presence of a high diastolic pressure and no renal involvement in a young patient. The other signs of retinitis (hemorrhages and exudate) which are nearly always present in malignant hypertension do not have the same significance as papilledema. Retinal hemorrhages are not uncommon in benign hypertension and extensive exudates are seen occasionally in elderly patients with diabetes.

Heymans⁶⁰ induced arterial hypertension in dogs by sectioning the cardio-aortic and carotid-sinus moderator nerves. The hypertension thus brought about

could be maintained for 9 to 26 months. It was found, however, that excision of the sympathetic paravertebral ganglionic chains from the stellate ganglia down to the pelvic ganglia prevents or causes the disappearance of this type of experimental hypertension.

Some abnormality of the urinary tract was found in 50 of 71 young persons suffering from essential hypertension by Schroeder and Steele.⁶¹ These abnormalities were demonstrated in pyelograms obtained after intravenous injection of diodrast. They concluded that it would seem desirable to explore further the meaning of these phenomena.

The emotional factors are often of considerable influence in producing hypertension. Menninger⁶² reviewed the histories of several cases in which essential hypertension had existed for some time and in which the blood pressure fell to normal after psychological technic had been employed. He states that it has been demonstrated that a passive conversational approach to a patient often releases some resentment (and hence some repression or fear) and this decrease in psychic tension should be reflected in a decrease in vascular tension.

Williams and Harrison⁶³ approach the subject of the relation between elevated blood pressure and renal arterial disease from the histological standpoint. They found that narrowing of the large renal arteries is related to advancing age. Narrowing of the afferent glomerular arterioles appears to be mainly the result of hypertension, and increasing age is a less important factor. Narrowing of the small renal arteries is related to both hypertension and increasing age. As age advances there is a decrease in the number of glomeruli per microscopic field, the change being more marked in hypertensive than in nonhypertensive subjects.

In a study of the acute arterial lesions in rabbits with experimental hypertension produced by clamping the renal arteries, Wilson and Pickering⁶⁴ found that the lesions were structurally identical to those of marked hypertension in man. These lesions were found throughout the body with the exception of the kidney to which the renal artery had been constricted. From this fact they concluded that a greatly raised intra-arterial pressure is the chief factor determining the acute arterial lesions in man.

Experimental work performed in an effort to establish the rôle of the adrenals in hypertension convinced Rogoff and Marcus⁶⁵ that existing experimental and clinical evidence is inadequate to support the theory that epinephrine excretion is a factor in the etiology of hypertension. The only exception seems to be certain types of adrenal medullary neoplasms.

In proof of the fact that renal involvement is not always the cause of and is not always associated with essential hypertension, Shapiro⁶⁶ reports the case of a woman who had a blood pressure of 220/110 for a period of 25 years. Although there were some signs of cardiac failure, death was due to a bleeding ulcer. Autopsy revealed no sclerosis of the arterioles or other pathology in the kidneys.

A study of the cardiac output in arterial hypertension was made by Holman and Page⁶⁷. In dogs whose normal range of cardiac output was known acute arterial hypertension brought on by constriction of the renal arteries produced no change in the cardiac output. Since the cardiac output remains unchanged, they concluded that arterial hypertension must depend on peripheral vasohypertonus.

Bundle branch block occurred in 36 (4.58 per cent) of Flaxman's⁶⁸ 786 cases with hypertensive heart disease. It ap-

peared to have no definite diagnostic or prognostic significance. The prognosis of the hypertensive patient with bundle branch block was that of the underlying heart condition, particularly in relation to the occurrence of congestive failure. There was, however, a close relationship between the bundle branch block and the congestive failure in the insufficient hypertensive heart. Gallop rhythm was present in only 5 (13.8 per cent) of the 36 patients showing bundle branch block, proving that there is no relationship between the 2.

In an investigation of the effect of epinephrine on normal and hypertensive persons, Fatherree and Hines⁶⁹ found that the magnitude of the rise in systolic pressure was the same in the 2 groups. In the patients with hypertension the diastolic pressure decreased more frequently than in patients whose blood pressure was normal. In both groups a change in diastolic pressure was always relatively less than the change in systolic pressure. There was no evident correlation between the effect of the cold pressor test and epinephrine on blood pressure.

Alam and Smirk,⁷⁰ using the application of cold to the skin and exercise of an ischemic limb to raise the blood pressure, found that the effect on both the systolic and diastolic pressure was less in patients with renal hypertension than in normal subjects in the same age group. However, the rise in blood pressure was relatively greater in cases of essential hypertension than in normal controls of the same age.

In discussing the management of hypertension, Stewart⁷¹ states that in his opinion none of the drugs directed toward lowering blood pressure are beneficial. A change in the mode of living is more valuable. One should attempt to have the patient lead a *restricted life* with *long*

hours of sleep, relaxation periods during the day, *frequent vacations* from business worries and removal of the worries themselves. Drugs such as *luminal* may be prescribed for the relief of persistent headache and to lower the level of hyperactivity.

It is the belief of Weiss⁷² that the *relief of anxiety* in the patient with essential hypertension is therapeutically much more important than a search for circulating pressor substances. This is not a complete solution to the problem and it is not applicable to all cases, but it is a "practical method of dealing with a set of important factors that may be modified whereas the constitution of the individual cannot be touched."

Since the work of Barker in 1936, the use of thiocyanate therapy in vascular hypertension has become more extensive. Massie, Ethridge and O'Hare⁷³ report the results in 14 patients suffering from uncomplicated vascular hypertension. They gave *sodium thiocyanate* in doses of 0.06 Gm for the first 4 to 5 days and then reduced the amount to 0.04 to 0.02 Gm daily. During the time of administration of the drug careful blood cyanate levels were obtained and the optimum was found to be between 5 and 7 mg per cent. This optimum was the lowest figure with which results could be obtained with the fewest difficulties. At higher levels toxic manifestations such as asthenia began to appear. Barker found the optimum to be between 8 and 12 mg per cent, but the authors state that it must be noted that in obtaining a desirable therapeutic effect, perhaps with greater reduction of pressure, he was not disturbed by the occurrence of slight toxic manifestations. The patient must be under strict observation and the blood cyanate level must be determined at frequent intervals so as to avoid toxic symptoms. In summarizing their results, they

found that a lowering of the blood pressure was obtained in all their cases. The average drop ranged from 66 to 21 mm. in the systolic pressure and 33 to 8 mm. in the diastolic. Marked symptomatic relief, especially from headache, nervousness and vertigo, was obtained in 12 of 14 patients.

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DISEASES OF METABOLISM

By JOSEPH I. BEARDWOOD, JR. A.B., M.D.

DIABETES MELLITUS

Mortality—E. P. Joslin, L. I. Dublin and H. H. Marks¹ report the observation which they have made on patients treated at the Baker Clinic from 1897 to 1928 and traced to 1929. They point out that up until now the only method available has been to compare the aver-

age duration of the disease from onset to death among diabetics in successive calendar periods. This method is not statistically correct, but as long as the conditions of treatment and the mortality rate of diabetics were fairly stable, the result served as an approximation of the truth.

The introduction of insulin caused a change in this picture and the average duration in the fatal cases of recent years is no longer measured by the longevity of the diabetic. Indeed, data on such fatal cases alone may give misleading results, for they possibly include a large number of patients who were neglected or poorly treated, or who died of accidents or acute emergencies. The tabulations which they made are in the same manner as those in insurance work. There has been a continuous decline in the death rate of diabetic patients; the death rate at all ages in the period 1926 to 1929 was 75 per cent below that of the first part of the study, 1897 to 1913.

The gains have been greatest in the young diabetic patients. The decline in mortality was most rapid after insulin came into use. Large increases in the expectation of life have occurred. At the age of 10, the increase between 1897 to 1913 and 1926 to 1929 is estimated at about 30 years. The increase is progressively less with advancing age. The death rate in diabetes is still much in excess of that for the general population.

Another independent article² comes to almost the same conclusions. In studying their cases from 1911 to 1937, they feel that the most direct and substantial effect has been the drastic reduction in mortality since 1922 among children and young adults. Among the children the actual number of deaths from diabetes has been so few in recent years that the variations in the death rates at these ages represent little more than chance fluctuations. Smaller declines were noted among males up to age 55 and females to age 35. Past these ages even with insulin there has been a gradual upward trend, and in women past 65 a marked increase.

The striking feature of this insurance experience is that the death rate when adjusted for changes in age, sex, and color make-up of the group has for the last 6 years been extremely stable, varying only from 20.5 to 20.8 per 100,000 between 1932 and 1937. This rate level however, is definitely above that prior to 1932. They feel that the important points contributing to the increasing incidence of diabetes is a more mechanized civilization with its abundant use of labor-saving devices in the factory, on the farm, and in the home, coupled with a liberal standard of nutrition, as a result of which there has been a continuous decline in energy spent in muscular work of the average individual. Another reason for the increased number of diabetics is the fact that the average length of life is greater and they tend to accumulate in the older age groups, and the mortality is therefore greater among the older individuals.

Seasonable Manifestations of Diabetes—R. Pannhorst and A. Rieger³ investigated the possible connection between the development of diabetes and the season of the year for 2 reasons. The first one was the frequent exacerbation in the metabolic condition of diabetic patients during the latter half of the winter and during spring, and the second one was the occasional statement of diabetic patients that they felt least well and capable during fall. However, in view of the multiplicity of factors that influence the carbohydrate metabolism of a patient who already has diabetes mellitus it would be difficult to ascertain whether the season of the year exerts a definite influence.

For this reason the authors decided to investigate whether a connection exists between the first manifestation of diabetes mellitus and the season. They investigated in this respect a material

of 719 diabetic patients; 392 were men and 327 were women. The graphic recording of the first appearance of the diabetes results in two entirely different curves for the male and female patients. Whereas the curve for the women shows only a slight rise in the fall and otherwise shows an even course, the curve for the men shows a slight decrease in the fall and a great increase during the winter. It occurred to the authors that perhaps the different age groups might participate in different degrees in the composition of the curve. The authors analyzed their material according to 4 different age groups and found that their assumption was justified.

After describing their observations on the relation between age and the seasonal fluctuations in male and female patients they emphasize that, in spite of these seasonal correlations, diabetes mellitus cannot be regarded as a seasonal disorder. They think, however, that periodic climatic processes act on the carbohydrate metabolism indirectly by way of the sympathetic nervous system. The authors call attention also to connections between diabetes mellitus and the endocrine glands.

Diagnosis—S. F. Seelg⁴ reports his results with an intradermal test in 51 patients, of whom 20 were suffering from diabetes and 31 were not. On the flexor surface of the arms of each patient, intradermal wheals were produced by the injection of 0.5 cc. of physiologic solution of sodium chloride and 0.5 cc. of a 0.1 per cent solution of dextrose. Results of the tests in the diabetic patients were uniform. In 19 of the 20 cases, the dextrose wheals disappeared more quickly than those caused by the saline solution. If one assumes that the time of disappearance of an intradermal wheal containing a certain substance which is a constituent of the blood is

indicative of the avidity of the skin for that substance, one may conclude that the skin of the diabetic has an increased avidity for dextrose. In no case in which diabetes was present did the dextrose wheal disappear at the same time or before that due to saline. This group of cases is too small to draw any definite conclusions and there was no statement in the article as to whether or not the diabetes was controlled at the time in which these tests were done. However, it is an ingenious test and might well lead to another diagnostic point in the appraisal of this disease.

Resistance to Staphylococcus Infection—A. Marble, H. J. White and A. T. Fernald⁵ report the results of tests on 23 nondiabetic patients and 27 diabetic patients in order to discover the inhibitory action and phagocytic power of the bloods on beta hemolytic streptococci. The results are essentially negative in that they show no significant difference between the bactericidal, bacteriostatic or phagocytic powers of the diabetic as compared with normal blood. Approximately the same variation of bactericidal or phagocytic power was found among the group of diabetic patients regardless of the duration, severity, or state of control of the diabetes as among the normal group selected at random. Diabetic patients who successfully combat past infections thereby develop specific immunity to roughly the same extent as do nondiabetic controls. They suggest the possibility that in the uncontrolled diabetic the hypercholesteremia which is present not infrequently may be associated with a blockage of the reticuloendothelial system and consequent lowering of its efficiency.

V. H. Richeri and O. Gomez⁶ feel, however, that partial immunity should be induced in diabetics by the administration of staphylococcus toxoid to pre-

vent the future development of pyogenic infection. The treatment consisted of 4 subcutaneous injections of 0.1, 0.2, 0.5 and 1 cc of a toxoid preparation of the National Institute of Bacteriology of Buenos Aires, giving it at intervals of 4 days. The antitoxic value of the blood serum shown by the concentration of antibodies is calculated in the usual manner. These authors found that the mechanism of immunity in diabetes is normal and the administration of toxoid stimulates the production which lasts more than 3 months.

Diabetes and Vitamin C—R. Pfleger and F. Scholl⁷ decided to determine how saturation with vitamin C affects the vitamin C metabolism of the carbohydrate metabolism of patients with diabetes mellitus. They accepted elimination in the urine as a measure of complete saturation. They determined the vitamin C deficit by means of the saturation method of Harris. They detected a hypovitaminosis in most diabetic patients; in some the deficit was as high as 2500 mg. After the normal biologic status had been attained, attempts were made to influence the carbohydrate metabolism. In diabetic patients who were not treated with insulin the cevitic acid exerted no influence on the sugar content of the blood and urine, but the combustion of the acetone bodies was favorably influenced.

After saturation with vitamin C, the action of insulin was noticeably intensified by cevitic acid, so that the carbohydrate metabolism of the diabetic patients could be regulated with smaller amounts of insulin. In persons without diabetes, saturation with vitamin C did not influence the fasting blood sugar or the blood sugar after tolerance tests. The sugar curves that were obtained after the administration of insulin revealed a noticeable intensification of the

insulin effect following saturation with vitamin C. The same effect, although in a milder degree, could be determined in diabetic patients.

As explanation of the increased responsiveness to insulin on the part of the organism that is saturated with vitamin C, the authors assume that the cevitic acid produces an increase in the capacity of liver to assimilate glycogen, or an increase in the tissue metabolism either directly or by activating the insulin. In all diabetic patients, irrespective of the modification of the sugar metabolism, cevitic acid improves the general condition; the fatigue disappears, the patient feels fresher and the vitality is increased. The authors direct attention to the vitamin C deficiency of the customary diabetic diets and stress the value of the medicinal administration of cevitic acid.

M. Oshima, T. Terashima and Y. Matsutani⁸ studied the influence of cevitic acid on the sugar content of the blood and urine in normal persons and in patients with diabetes mellitus. They found that in healthy subjects the intravenous injection of 300 mg of cevitic acid did not influence the blood sugar curve. In diabetic patients, however, the injection of 300 mg of cevitic acid produced nearly always a reduction of the sugar content of blood and urine. The authors report 4 cases of diabetes mellitus in which they resorted to treatment with cevitic acid. In one of them the blood sugar was comparatively low and the urine was free from sugar. In this mild case of diabetes the effect of the cevitic acid was not so noticeable as in the other cases.

Diabetes and Pregnancy—W. W. Herrick and A. J. B. Tillman⁹ report their experiences with 67 pregnancies and 56 diabetic patients in a very comprehensive paper. They point out that

severe diabetes often affects the reproductive function adversely, but that when it is controlled, the fecundity of the severe diabetic approaches normal.

Diabetes with onset during pregnancy presents a difficult diagnostic problem for a number of reasons; the metabolic equilibrium of the pregnant woman is relatively unstable. In addition to the disordered carbohydrate metabolism there is an increased metabolic rate averaging 14 per cent in the last trimester and a tendency for diminished alkali reserve and acidosis. There is also apt to be a depletion of the glycogen store, a hypoglycemia and a lowered renal threshold. Even in the nondiabetic pregnant woman, the sugar tolerance curve may be suggestive of diabetes, so that it is only after careful study that an actual diagnosis of diabetes can be made.

In their cases, 17 of the 56 gave a family history of diabetes. Five showed hyperthyroidism. The age range of onset of diabetes varied from 15 to 38 years. The previous obstetrical history showed an extraordinary number of stillbirths, miscarriages, or infants that died immediately after birth.

The antepartum complications in this series are especially interesting, particularly the greater liability to late toxemia. Twelve of these patients showed evidence of a complicating toxemia. In regards to the size of the fetus of the diabetic mother, it is the experience of these investigators that the child is just as likely to be underweight as overweight, and in none of these was cesarean section necessary because of the diabetes alone. In regards to treatment they point out that the diabetic presents several therapeutic pitfalls. The vomiting of early pregnancy augments the danger of diabetic acidosis and the authors use a diet containing 200 Gm. of carbohydrate a day in all of their patients. This was

given in 5 or 6 feedings at 2-hour intervals and insulin given as frequently as necessary. When the early toxemia was controlled, these patients were put on a diet which attempted to limit the gain of weight during pregnancy to 25 pounds.

The second trimester, once regulation has been established, usually presents little change in the basic requirements of diet and insulin. In the last trimester, however, marked changes in tolerance are to be expected. These vary in degree and in time of appearance for which no adequate explanation can be given. It is important to watch the patients carefully during this period. They feel that acidosis is a greater threat to the fetus than hypoglycemia, and of the 5 patients with acidosis 4 had stillbirths or miscarriages. Fourteen of these patients had severe hypoglycemic reactions and all 14 bore living babies.

Labor and puerperium give rise to peculiar problems in the diabetic. Twenty-five of the 67 pregnancies were delivered spontaneously, 16 by instrumentation. There were 15 fetal deaths in this series of which only 6 were contributed to diabetes alone. There were no maternal deaths in this series, and these writers feel that cesarean section is not indicated because of the diabetes itself or because of fear of a large baby.

E. Brandstrup and H. Okkels¹⁰ report their experiences with 22 instances of pregnancy in 19 diabetic patients at the Lying-in Department A, Rigshospital, Copenhagen. This material is not suggestive of any change in the diabetic condition of the mothers during pregnancy. The restitution of these patients after the puerperium indicates that such changes as have been observed during pregnancy (frequency of acidosis and changes in the insulin requirement) are attributable to factors of a nature that does not directly concern the diabetic condition. The ob-

stetric risk is somewhat increased through a tendency to hydramnios, excessive size of the child and, especially, infection in the presence of eczema of the vulva.

In the 22 cases observed, only 10 living children were discharged from the hospital. The great mortality among children of diabetic patients may probably be attributed to maternal hyperglycemia and acidosis. In 3 of the dead children the necropsy was extended to include a thorough microscopic examination of the endocrine organs. The pathologic changes observed in the pancreas, hypophysis and thyroid are described

Commenting on these changes, the authors say that the maternal hyperglycemia alone brings about the pathologic changes in the child. In the discussion of the therapeutic problems, it is pointed out that in the future the main task of the treatment should be to employ such dietetic and medicinal measures as to make obstetric operations unnecessary. The pregnant diabetic patient must be watched closely, and the efforts must be aimed at the avoidance of hyperglycemia and acidosis. The therapeutic significance of protamine zinc insulin is emphasized.

The Obese Diabetic Patient — F. Better, J. K. Durkin and G. G. Duncan¹¹ report their observations on the obese diabetic. They feel that the average obese diabetic, regardless of the initial blood sugar or urinary findings, can often be satisfactorily standardized without insulin if the weight is brought to normal. These patients are put on a low caloric diet before instituting insulin treatment. If there is no weight reduction in this group, the insulin requirements are apt to be very high. This work is rather interesting, but the number of cases presented is too small to draw any very definite conclusions, and, as the authors point out, a patient who needs insulin

should receive it promptly and possibly at a later date it may be discontinued.

Complications — Relief of pain of neurocirculatory origin was attempted by H. R. Sandstead and A. J. Beams¹² by the administration of from 15 to 90 Gm. daily of *sodium chloride* to diabetic patients whose pain had not been relieved by the usual diabetic management. The pain was said to be of neuritic origin in 10 cases, and of arteriosclerotic origin in 33. All of the patients obtained complete or marked relief of the symptoms after the administration of salt. This relief was accompanied by signs of improvement in the circulatory condition as shown by the histamine test. They feel that the oral administration of sodium chloride is the rational treatment for neurocirculatory pain in the diabetic.

Tuberculosis in Diabetes — H. P. Himsworth¹³ found 15 (6.5 per cent) cases of tuberculosis in 230 consecutive diabetics on their first attendance at the hospital. Two of these patients had tuberculous bronchial pneumonia and were readily diagnosed by clinical methods. In the remaining 13 the diagnosis was made only by x-ray examination and the conclusion is drawn that early pulmonary tuberculosis in the diabetic is impossible to diagnose by clinical methods, and that a routine x-ray examination should be made in every diabetic patient when he is first seen. The x-ray appearance of early pulmonary tuberculosis in diabetes is that of a chronic inflammatory lesion. He feels that uncontrolled diabetes predisposes to the development of pulmonary tuberculosis, but that well-controlled diabetics are no more liable to contract the disease than nondiabetics.

Pilgerstorfer¹⁴ reports that of 1208 patients with diabetes at the University of Vienna from 1923 to 1936, 71, or 5.8 per cent, had pulmonary tuberculosis. *Pneumothorax* treatment produced favor-

able results only in the early cases. The author feels that a *high carbohydrate diet* is the most valuable therapeutic method for such patients, and that the protein and fat content of the diet seems to be of no significance in the prognosis.

E. P. Ralli and I. Steinberg¹⁵ report that in 748 patients attending the diabetic clinic at Bellevue, 33 had active pulmonary tuberculosis, and in 29 of these the diabetes preceded the tuberculosis. Thirteen of the 33 patients followed have died since acquiring tuberculosis. These authors found it advisable to give feedings 4 times in 24 hours, and to give insulin with each feeding. They feel also, that an intake of at least 90 grains (6 Gm.) of salt a day is necessary, as well as a generous water and calcium intake.

Succinic Acid in Diabetic Ketosis

—There have been conflicting reports in the recent literature concerning the effects of succinic acid in the treatment of diabetic ketosis. F. Mueller and H. Buchwald¹⁶ report the results of their investigation on this problem. They determined the ketone content of the blood and urine of patients who were given succinic acid over a considerable period of time, and concluded that succinic acid has no effect whatsoever in diabetic ketonemia.

Oral Aspects—A. Rudy and M. M. Cohen¹⁷ report studies on the oral manifestations of 403 diabetic patients. Of these, 138 presented edentulous mouths. In the younger children of this group, the eruption of permanent teeth was normal and in correct relation with their age. They feel that as a general rule the adult, dentulous, medically controlled patients who were examined presented mouths which were unclean, owing to lack of oral hygiene with heavy deposits of both supragingival and subgingival calculus. Roentgenographically and clinically this group has a high incidence of diffuse alveolar atrophy. This is par-

ticularly true of the younger age group (25 to 45), in which diffuse alveolar atrophy is not generally attributed to local causes. Patients with acute or inadequately treated diabetes present a characteristic oral symptomatology. It is manifested clinically in the gingival papillae, which become markedly swollen and tender and bleed profusely on the slightest pressure. These patients also present loosening of the teeth. This is associated with pain, especially on percussion. With control of the diabetes the acute inflammatory condition of the gingiva subsides, the loosened teeth become fixed and pain on percussion disappears. Extraction of teeth in the inadequately controlled diabetic patient results in a prolonged period of suppuration and pain. Local treatment without attention to the diabetes is futile. Infected teeth may aggravate the diabetes and should therefore be removed. Extraction of teeth should be carried out only on controlled diabetic patients and under the supervision of a physician. Neglect may result in serious complications.

Insulin—There is a large and growing accumulation of literature on the use and advantages of the longer acting insulins in the treatment of diabetes. An appraisal of these articles which are too numerous to enumerate here show that the initial enthusiasm as to the extent to which these newer insulins could be substituted for the old has been supplanted by a practical knowledge of their indications as well as their limitations. There are at the present time available to the physicians treating diabetics 2 insulins which have a prolonged action, namely protamine zinc insulin and crystalline insulin.

Protamine Zinc Insulin—It has been said (*Advances in the Treatment of Diabetes*) that its advantages are manifold. Its greatest prospective value is

that it can give easy and effective control of the disease in large numbers of mild diabetics who hitherto have not used insulin. The use of protamine zinc insulin demands careful study and observation by the physician and intelligent co-operation of the patient. Protamine zinc insulin brings the patient 1 step closer to normal living because it usually need be taken but once a day.

Most new patients adjust themselves easily on protamine zinc insulin. The older patients may not adjust themselves quite so readily. They require a great deal of study on the part of both physician and patient in such cases, and one must not be discouraged by failure due to difficulties in readjustment in these patients.

Reactions may occur with protamine zinc insulin, but with a different train of symptoms from those with regular insulin. Physicians and patients must learn to recognize the symptoms and they may, in many cases, be avoided by proper adjustment of insulin, diet and exercise.

E. P. Joslin¹⁸ points out that protamine zinc insulin has probably increased the number of diabetic patients using insulin in the United States by 70,000. This has come about not because of what doctors have said concerning it but because diabetic patients generally recognize the value of insulin, and the simplicity of taking it only once a day has encouraged many to use it who avoided it heretofore. The fact that during the brief period of 1 or 2 years the number of insulin users has increased so much demonstrates that the problem of the management of diabetes in this country is changing rapidly. And there is good reason for this change. The rising incidence of diabetes in the United States is due first of all to the more systematic search for diabetic patients and the closer medical supervision of the population in

general; secondly, many more people now live beyond the age of 40 years, thirdly, diabetic patients live much longer than they used to. Two other factors may be the changing diet and the lessened participation in muscular work.

One of the commonest errors is to expect results from protamine zinc insulin within the first few days of administration. A diabetic patient has 20 years or more ahead of him and one need not hurry. It is safer to proceed slowly. One must allow time for it to act and actually more time is demanded to change a patient who has been living on regular insulin to protamine zinc insulin than is necessary to start a fresh patient on protamine zinc insulin.

B. Greenhouse¹⁹ feels that he has noticed an increased carbohydrate tolerance of diabetic patients to whom he has given protamine zinc insulin. This he attributes to the continuity of effect and prolonged action. He points out that it furnishes a basic insulin supply by creating a depot from which insulin is regularly and continuously liberated so that the body has available a supply of insulin at all times over a period of at least 24 hours. The metabolism of the diabetic patient is thus more adequately stabilized, offering particular respite to the pancreas and liver. He feels that protamine zinc insulin finds its greatest usefulness in the case in which the diabetes is in part at least functional, rather than in cases of diabetes in which the pancreas is so sclerosed as to allow for no improvement. Improvement occurred most frequently in the large middle-aged group of patients.

Crystalline Insulin—Crystalline insulin, first developed by Dr. Sayhoun in 1935, is now available as a solution of insulin crystals, and has a definite prolongation of action of about 12 hours, and shows this difference possibly be-

cause it is a solution of insulin crystals and not amorphous insulin. The zinc content of this insulin is now 2 mg. per 1000 units, and recent work by S. S. Altschuler and R. Leiser²⁰ has shown that this is as efficacious as any of the previously tested solutions of insulin crystals, also that it is much more prolonged than that of regular insulin. This solution is a clear solution and does not give any local reaction. When a hypoglycemic reaction does occur it is more apt to be like that of regular insulin than the reaction occurring with protamine zinc insulin. Many mild cases of diabetes can be satisfactorily standardized with a single injection and most severe cases with 2 injections of this insulin a day. The dose of crystalline insulin must be determined for the individual patient but is usually about 80 per cent of that of regular insulin.

Resistance to Insulin—There have been in literature, from time to time, articles concerning cases which are listed as "Insulin Resistant" because of the fact that very large doses of insulin seemed to produce no marked change in the blood sugar. R. Herbst²¹ reviews the situation and states that a patient can be regarded as resistant to insulin only if, after an injection of insulin, the blood sugar is reduced less than is generally the case under comparable conditions. He points out that glycosuria in spite of the reduction of the blood sugar is caused by the reduced renal threshold, and states that only a great increase in the action of epinephrine may temporarily impair the function of insulin. He feels that the most common reason for resistance is either fever or acidosis and that in acidosis the proper treatment of the acidosis will result in greater utilization of the insulin injected. This author does not state that in acidosis the reason for the insulin resistance is a change in

the pH of the tissue which temporarily inactivates the insulin which prevents it reaching the cell in which insulin activity is greatest. The author would like to state that "Insulin Resistance" is a very poor term and that there have been reported in literature very few cases which might be listed in this category. It is probably true that a unit of insulin will vary in its efficacy in different patients, but the same is true of experimental animals which theoretically present the purest and most uncomplicated type of diabetes.

USE OF INSULIN IN MALNUTRITION

S. Dorst²² reviews the work done with the use of small doses of insulin in nondiabetic patients for the purpose of gaining weight. He points out that the early results with this method of treatment have seemed favorable but as a larger series was studied, it became obvious that certain groups of underweight individuals did not respond to insulin treatment. Following this, enthusiasm waned, and the treatment fell into discredit in many clinics. He undertook to determine beforehand which patients could be benefited by this treatment, and found that patients fell into 2 groups.

The first group showed what is usually accepted as a normal glucose tolerance curve with a rise of 80 to 140 mg per cent above the fasting level after the administration of glucose and a rapid drop to a figure slightly below the fasting level between 2½ to 3 hours, then a subsequent rise to the fasting level. The second group showed a fasting level which might be considered below normal. After the administration of 3½ ounces (100 Gm.) glucose by mouth, the curve remained between 90 and 100 mg throughout the 3 hours. They point out that these types of curves have been

thought to indicate a hypopituitarism and they feel that possibly that may be the fault in producing this picture.

To individuals in the latter group they administered insulin as follows: 5 units before breakfast, 10 units before lunch and 10 before dinner which was administered 15 minutes before meals. The patients were then allowed to select their own diet and found that in spite of these patients having a low sugar, shortly after beginning of the insulin treatment they began to feel better; nervousness, irritability and asthenia disappeared and the glucose tolerance curve rose to normal limits. They also found that if 2 months afterward the insulin was suddenly withdrawn, patients tended to have a return of symptoms, whereas if the withdrawal was gradual they maintained normal health. This condition must not be confused with hyperinsulinism. It is possible that in these cases the demobilization of hepatic glycogen is in some way inhibited and that the insulin restores this to a more normal cycle.

OBESITY

The treatment of obesity, whether it be so-called endocrine or not, obviously has as its basis a regulation of energy exchange between the food ingested and the metabolic demands of the patient, and it is obvious that if a patient is placed on a suitable caloric diet and adheres to that diet, weight loss must result. A difficult thing is oftentimes the patient himself who unconsciously digresses from the program by taking small feedings, indeed, many of these patients, in spite of strenuous efforts, are unable to adhere to the diet.

M. F. Lesses and A. Myerson²³ feel that the obese individual presents very definite psychological status, in which nibbling of food and indulgence in other

ways have become so much a part of the personality that a reflex of a satisfied appetite is lost, and that these people continue to eat as a source of nervous energy release. They point out that many of these people are depressed and fatigued even after eating and theoretically at a time in which their energy should be greatest. They suggest a novel approach to these patients and in their hands it has proved to be of considerable value. They are placed on a relatively low caloric diet but no great effort is made to emphasize the importance of their co-operation. They then give them, at meal time, small doses of *benzedrine sulfate* which has the effect of producing a euphoria and also the physiological effect of reducing irritability of the gastrointestinal tract, and delaying the emptying time of the stomach. They gave these patients about $\frac{1}{9}$ gram ($7\frac{1}{2}$ mg) in the morning and $\frac{1}{12}$ grain (5 mg) at the other meal times. This does not result in central stimulation and insomnia. On this regime they found that the patients felt better, that their co-operation was greatly improved and that they lost on the average of 1 pound to $1\frac{1}{2}$ pounds a week. Benzedrine has no effect on the metabolism *per se*, but evidently helps overcome the psychoneurotic state which is the cause of their hyperalimentation and obesity.

D. Embleton²⁴ reviews the result of dextrose tolerance curves in 500 obese cases (242 males and 258 females). He does not give any example of gross endocrine disturbances. Only a small percentage of these showed sugar in the urine. The most striking result of this test is the difference between the obese of the 2 sexes. The men show a total of 73 per cent high curves for all ages, whereas the women show only 35 per cent of high curves. If this is plotted out according to the age group, it is still

more striking. Most of the males below 35 years showed a low dextrose tolerance curve. After this age a sudden rise occurs so that between 35 and 45 nearly 80 per cent of obese men show a high dextrose tolerance curve, after which this high level is maintained up to the age of 65 and beyond. The women, however, showed a greater tolerance curve after 45 but the highest level was not reached until 55 to 65 years. He found as a possible explanation that, at autopsy, the women showed normal muscles encased in layers of fat, whereas in the men the musculature was heavily infiltrated with fat.

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NEUROLOGY

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CHOREA

By MANUEL SALL, M.D.

In the past year *fever therapy* in the treatment of chorea has received more and more attention, other modes of therapy having been employed to a much less degree. While fever is still being induced by the use of *typhoid-paratyphoid vaccine*, the method of choice more recently recommended seems to be *high frequency currents*. Of the drugs used in the treatment of chorea Nirvanol has been practically discarded. Sulfanilamide has been employed but is of no value in the treatment of chorea. For

the more severe cases where the danger of life is feared, *somnifene* and *magnesium chloride* have been used with success but only in a few cases.

Treatment—C. H. Barnacle, J. R. Ewalt and F. G. Elbaugh¹ induced *fever* in 45 cases of chorea by means of the Kettering hypertherm and reported excellent results. Forty of these cases were followed over a 2-year period. The patients were given daily treatments for 2½-hour periods at temperatures ranging from 105° to 105.4° F. (40.5°

to 40.7° C.) rectal. Strict rest was enforced during treatment and restricted activity was observed following the course of the fever. The average number of treatments was 12.6, the total hours of fever 32.9 and the average treatment periods 22.3 days. The more severe the case, the greater the number of treatments required. Rheumatic carditis was no contraindication to fever therapy nor did it bear a relationship to the number of treatments required. Signs of carditis cleared up more rapidly with the treatment. It was found that the treatment did not interfere with weight or appetite. Of the 45 cases treated, a great majority had failed to respond to the more conservative methods of therapy. With the fever treatment, 37 cases recovered and 8 were markedly improved. Of 40 cases followed over a 2-year period there were found to be but 4 recurrences.

The excellent effects of electrically induced fever in the treatment of chorea was also demonstrated by S. L. Osborne, M. L. Blatt and C. A. Neymann.² Artificial fever was induced by the electromagnetic induction coil in 25 cases with disappearance of the choreiform movements in 88 per cent of the cases. The authors also made careful electrocardiographic studies and found that artificial fever thus induced did not adversely affect the normal heart or the cardiovascular system if the doses of fever were those normally employed for the treatment of the disease. They also demonstrated that carditis and other forms of heart disease were not adversely affected by artificial fever if the heart was not decompensated.

The question as to the lasting effects of typhoid-paratyphoid induced fevers in the treatment of chorea was investigated by E. P. Sutton, and K. G. Dodge.³ Ninety-nine cases were followed

after treatment for periods ranging from 1 to 6 years. Sixty untreated cases were used as controls. They found there was a recurrence of chorea in 36 per cent of the treated cases and in 44 per cent of the untreated patients. The most striking differences were found in the occurrence of polyarthritis; (6 per cent in the treated group and 32.5 per cent in the untreated; and in deaths from heart disease (23.8 per cent in the treated and 16.9 per cent in the untreated).

A. de Grissac and L. Rabinovitch⁴ successfully treated a severe case of chorea gravis by the intravenous administration of *magnesium chloride*. The patient, a 19-year-old male, was gravely ill. He had failed to respond to the usual modes of therapy. Magnesium chloride 1 grain in 10 cc. of distilled water was administered intravenously every other day. After 5 injections, the patient was improved sufficiently to feed himself and after the tenth injection was considered cured. However, an injection was given every fourth day for a few injections to make certain of the cure. Frequent urinalyses were negative. The patient was seen on several occasions after discharge with no signs of recurrence. The injections are not painful but are attended with a sensation of intense heat, with redness of the face and vasodilatation. These symptoms are transitory and disappear rapidly.

M. M. Riser, Laboucarie and Geraud⁵ successfully treated 2 cases of chorea gravis with *somnifene*. Both patients had severe chorea with encephalitic syndromes. The usual methods of therapy having failed, they were given 5 cc. of *somnifene* intravenously, resulting in immediate sleep and cessation of involuntary movements. This lasted 12 hours, after which the movements recurred but with greatly decreased severity. The in-

jection was repeated in 1 patient when it appeared that the chorea was about to recur. The patients made a good recovery with supplementary treatment of the usual type.

B. F. Massell and T. D. Jones⁶ employed sulfanilamide in the treatment of 58 cases of rheumatic fever. Seven patients had an active chorea. The sulfanilamide was administered in divided doses with a total daily dosage of approximately 6 grains per 10 pounds (0.08 Gm. per kg.) of body weight during the first 24 hours and thereafter 4

grains per 10 pounds (0.05 Gm. per kg.) of body weight. Treatment was continued from a few days to as long as 2 months. This treatment had no effect upon the natural course of the chorea in any of the 7 cases. Toxic effects from the use of the drug included severe febrile reactions, particularly in those cases with an active rheumatic fever and widespread rash. These facts, together with the lack of any beneficial results, makes the administration of sulfanilamide *contraindicated* in the presence of active rheumatic fever.

CRANIAL TRAUMA

By ELI MARCOVITZ, M.D.

Treatment - There seems to be an increasing tendency towards conservatism in the management of cases of cranial trauma, with limitation of surgical intervention to those cases where there is a depressed fracture, or where there is a suspicion of a mass collection of blood or fluid.

In a general survey of the treatment of cerebral trauma, Temple Fay⁷ discusses the importance of insuring an optimal oxygen supply to the injured tissue, by increasing the blood supply at the expense of cerebrospinal and tissue fluid. He depends on pulse pressure as the most important index of the state of oxygen delivery to the brain. A rising pulse pressure indicates increasing cerebral anemia and should be counteracted by lumbar puncture or spinal drainage. A falling pulse pressure warns of the danger of vasomotor failure, usually secondary to profound cerebral anemia. This situation requires more heroic measures, *i. e.*, **spinal drainage**, **administration of hypertonic solutions** by vein or bowel, and even **decompression**. In

addition, **cardiovascular stimulants** may be required.

The author believes **subarachnoid hemorrhage** should be treated by repeated **spinal punctures**, both to remove the blood which is an irritant to the meninges and interferes with spinal fluid production and absorption, and to help in arrest of hemorrhage. Contrary to the usual opinion that removal of spinal fluid may prevent clotting by releasing pressure, he argues that spinal fluid is an anticoagulant and should be removed. Furthermore, it is useless to depend on the intracranial pressure to stop bleeding, because the bleeding is frequently arterial, and a pressure sufficient to stop bleeding would have to compress the entire arterial tree, to the detriment of the brain as a whole. He has found that, when subarachnoid bleeding continues, 5 to 20 cc. of **air injected into the spinal subarachnoid space** promotes immediate clotting.

Fay also discusses the use of **hypertonic glucose solution**, and feels that it can be used without fear of the second-

ary edema which occurs, if consideration is given to the state of the blood volume. During shock, glucose increases the low blood volume. After 1 or 2 injections of glucose the blood volume is usually full, and before glucose can be used again the blood volume should be decreased by the limitation of fluids and the administration of *magnesium sulfate* by bowel or by mouth. The pulse rate is a fair index of blood volume. Usually "when the pulse rate is over 120 it is the cry of the circulation for more volume."

Nicholas Gotten⁸ reports on 141 consecutive cases of head trauma, with a mortality of 10.6 per cent. On analyzing the age incidence he found that in the cases under 20 years of age the mortality was only 5 per cent. Between the ages of 20 and 60 the mortality was 10.6 per cent, but over the age of 60 it was 33.3 per cent. In this series there were 7 operations, with a mortality of 42.8 per cent. The author recommends initial treatment for shock, then examination, and lumbar puncture for diagnosis of pressure and bleeding. He does not recommend the routine repetition of lumbar punctures unless the pressure is elevated. He advises *dehydration* by limitation of fluids to 900 to 1200 cc daily and the administration of *magnesium sulfate* and *lumbar puncture* when necessary. Operative intervention is indicated,

in his opinion, only in the presence of a depressed fracture or in suspected mass hemorrhage.

A discussion based on 81 cases operated on following head trauma is given by E. S. Gurdjian.⁹ He has found that in middle meningeal hemorrhage there are usually neurologic signs implicating the cortex on the affected side, and dilatation of the pupil on the same side. Occasionally the pupils are equal, and in 1 case the opposite pupil was dilated. All cases of middle meningeal hemorrhage had bloody spinal fluid. Although in these cases a lucid interval is usually found, it may be absent because of very rapid hemorrhage or because of associated severe damage of the brain. A lucid interval may also occur in other conditions as in acute subdural hemorrhage, a subdural collection of spinal fluid, and edema of the brain. The author believes that *exploratory craniotomy* following trauma is indicated by a combination of all or some of the following signs: (a) Dulling of the conscious state, leading to unconsciousness or progressive deepening of an unconscious state already present; (b) the presence and progression of localizing signs rather than signs implicating the entire nervous system; (c) an increase in spinal fluid pressure, and (d) a low pulse rate in some cases.

ACUTE ENCEPHALITIS

By HENRY A. DAVIDSON, M.D.

Differential Diagnosis—In its early stages, acute lethargic encephalitis may clinically resemble St. Louis encephalitis, Australian "X" disease, Japanese encephalitis, and even poliomyelitis. The best differentiation, according to Web-

ster,¹⁰ is established by laboratory tests, performed by examining serums of convalescents for specific neutralizing properties against one of the virus agents, or by securing virus from the brain tissue of fatal cases and testing its effect

on laboratory animals as well as its neutralizing properties with reference to specific antiserums.

Prognosis—Holt¹¹ found in a follow-up study of 240 patients who had epidemic (von Economo) encephalitis during the epidemic years (1917 to 1926), that 11.5 per cent were alive, well and free of sequelae after an average interval of 13 years. The actual proportion of complete recovery, however, must have been much higher since these figures referred to the patients who were ill enough to require hospitalization during their primary encephalitis. The prominence of psychic symptoms during the attack did not appear to alter prognosis. However when sequelae developed, the hope for improvement was much less. Children with behavior disorders were the only group with sequelae in whom improvement was frequently found. For the St. Louis form of encephalitis, Bredeck¹² and his colleagues found a general mortality of 18.7 per cent. Of all the available patients who had had this illness, a total of 66 per cent felt that they had experienced no impairment of health as a result of the encephalitis.

Encephalitis and the Exanthemata The occasional occurrence of encephalitis after vaccination or in the course of measles, mumps or other exanthemata has long been known, and is little understood. Finley¹³ advances an *allergic* explanation. Thus, in vaccination as part of the tissue reaction, antibodies appear by the fifth day and a specific precipitin response can be demonstrated by the eighth day. The incubation period of postvaccinal eruption corresponds to the height of the body's specific reaction to the invader. When encephalitis develops, its incubation period is consistently between 10 and 12 days, so that the onset of cerebral symptoms coincides with the maximum tissue

reaction. This suggests that the same biologic forces provoke the vaccination wound, the exanthem, and the brain lesions. Similarities between the clinical and biologic features of smallpox and measles encephalitis suggest a similar type of tissue behavior. By this hypothesis, the brain reaction is regarded as an allergic response to the virus of the exanthem. Supporting this thesis, Gareiso and Sagreras¹⁴ demonstrate that encephalitis develops within 2 or 3 weeks in the course of whooping cough and in from 4 to 6 days in the course of measles. They believe that the cerebral lesions are caused by the toxic effects of the virus. Finkelstein¹⁵ stresses the frequency of mild, often subclinical, encephalitic involvement in mumps. He examined routinely the spinal fluids of 40 children suffering from mumps and found spinal fluid abnormalities suggestive of encephalitis in 16 of them (40 per cent). In few cases, however, was there any clinical manifestation of cerebral involvement. Like Gareiso and Sagreras¹⁴ he believes that cerebral lesions in the exanthemata are due to a virus, and quotes Neal, who thinks that the same virus causing the mumps also causes the encephalitis. Experimental evidence of the basic pathology of exanthematous encephalitis is offered by Hoefler, Putnam and Gray.¹⁶ In laboratory animals, they introduced intravenous coagulants and by provoking thrombosis of small cerebral vessels were able experimentally to reproduce encephalitis of the type associated with the exanthemata. If sublethal doses of coagulants were administered, many of the animals survived but gave clinical evidence of encephalitis.

Equine Virus Encephalitis—Two epidemics of encephalitis due to the equine virus were reported in 1938. Fothergill and his associates¹⁷ recorded

an outbreak in Massachusetts, while several other cases in the same area were cited by Wesselhoeft, Smith and Branch¹⁸. A western outbreak occurred in Minnesota and was reported by Ek-lund and Blumstein.¹⁹ From the brain of one of the victims of the Massachusetts series, Webster and Wright²⁰ were able to isolate the virus. Olitsky and Harford²¹ describe a technic for testing and identifying the equine strain by injection into mice. In the Minnesota cases, the death rate was 33 per cent. The fatality ratio is not reported for the Massachusetts outbreak. The diagnosis seems possible only with serum neutralization tests. In the Minnesota cases, most of the patients had had contact with sick horses. The victims of the Massachusetts outbreak had had no actual contact with horses, but all lived in an area where horses had been stricken. Clinically the disease presents itself as a fulminating encephalitis with a high fever, abnormal spinal fluid, and marked leukocytosis. The possibility that mice may act as a carrier has not been excluded.

Treatment—The only 1938 report on the treatment of acute encephalitis is that made by So,²² who secured good results by injecting patients with the *serum of normal persons*. The serum is not inactivated and is injected intraspinally while fresh. From 3 to 8 cc is introduced into the lumbar subarachnoid space. In most cases temperature promptly fell to normal, and mental symptoms improved.

Postencephalitic Parkinsonism

Traumatic Parkinsonism — While the possibility of traumatic precipitation of the paralysis agitans syndrome is no longer doubted, Chichilnisky²³ stresses the data for making this assumption. His criteria are: (a) No history of en-

cephalitis; (b) history of head injury, usually severe but not necessarily accompanied by unconsciousness; (c) an incubation period beginning with the date of the trauma and running for several months thereafter; (d) progressive evolution of the paralysis agitans picture beginning with the end of the incubation period. Hemorrhagic lesions in the basal ganglia account for the condition. That peripheral trauma as well as head injury may precipitate parkinsonism is suggested by Main,²⁴ who cites a case of trembling of the fingers beginning 5 weeks after a finger injury. In this patient the trembling spread, eventually leading to a typical paralysis agitans picture. The relationship between the finger injury and the parkinsonian syndrome was, in Main's opinion, etiologic rather than coincidental.

Vesical Abnormalities—The urinary frequency which often accompanies parkinsonism is explained by Langworthy²⁵ as due to a lessening of bladder capacity because of the release of the reflex pathways which, mediating through the affected midbrain, would ordinarily control the tone of the detrusor muscle. Other factors are the increased intra-abdominal pressure of the agitated paralytic and the general muscle hypertonicity.

Treatment of Parkinsonism—In addition to the *hysocine* and *stramonium* treatment commonly used in the United States, 3 other therapeutic agencies have been reviewed during 1938. These are benzedrine, atropine, and cobra venom.

Benzedrine—Favorable results with the use of benzedrine sulfate (benzyl methyl carbamate) are reported by Matthews²⁶ and by Davis and Stewart.²⁷ Matthews found definite and sustained improvement in 15 out of 20 patients (75 per cent) which was attributed to

the benzedrine, since the previous drug régime was supplemented but not replaced. The benzedrine should be used in addition to (and not instead of) *atropine*, *stramonium* or *hyoscine*. Davis and Stewart²⁷ used benzedrine on 74 advanced hospitalized cases. Patients having a systolic blood pressure below 130 received 60 mg. a day (3 tablets twice a day) while those whose systolic pressures exceeded 130 received 40 mg a day (2 tablets twice a day). The results were very encouraging and several previously helpless patients were able to feed themselves. Subjective improvement was reported by 66 of the 74 patients (88 per cent). Objective improvement could be confirmed in 53 cases (71 per cent). Of 23 sufferers from oculogyric crises marked improvement was found in all the cases. Matthews found improvement in 5 of his 6 victims of oculogyric crises. Improvement in handwriting was seen in 72 per cent of the patients. Tremor was visibly reduced in only 30 per cent of the cases.

Cobra Venom Cobra venom relaxed the rigidity of parkinsonism in 7 cases reported by Macht²⁸ and in 12 reported by Gayle and Williams.²⁹ The recommended dose is 0.5 cc intramuscularly the first day and a full cubic centimeter every other day thereafter for 10 days. In patients showing improvement, the interval between injections is lengthened.

About a third of the patients fail to respond, and, in these cases, injections are discontinued after the tenth treatment.

Atropine—The usual method of administering atropine sulfate is in a 0.5 per cent solution, starting with 3 drops a day and increasing a drop a day to a maximum of 40 or 50 drops daily. A drop of this solution contains $\frac{1}{250}$ gram or 0.25 mg of atropine. Grewel³⁰ recommends that, as a rule, the daily atropine dosage be kept below 10 mg (40 drops of the 0.5 per cent solution), though in exceptional cases he has used as much as 35 mg (140 drops) a day. Instead of the 0.5 per cent solution, Broekema³¹ uses an extract of the root and root-stock of *atropa belladonna* containing 0.02 per cent alkaloid. He begins with 2 cc and gradually increases the dose. The average maximum daily intake varies from 60 to 120 cc. His results were almost uniformly good, though Grewel³⁰ is disappointed in the persistence of the speech disorders and the in-co-ordination. Both he and Broekema,³¹ however, noted marked improvement in the tremors, the facial immobility, and psychotic symptoms. Gandellini³² prefers a 5 per cent decoction of *atropa belladonna* in white wine. The dosage is 5 to 15 cc 3 times a day according to the patient's age. He found improvement in 120 out of 150 cases, an improvement rate of 85 per cent.

EPILEPSY AND THE CONVULSIVE STATE

By HENRY A. DAVIDSON, M.D.

Physiology—The importance of hypoglycemia as a factor in provoking convulsions is doubted by Hirschfelder and Haury³³ who find no change in the spinal fluid chemistry during a paroxysm. The plasma potassium increases and

plasma magnesium decreases, during the spell, but no spell is provoked by administering magnesium or by reducing the potassium intake.

The chief weapon for the investigation of the physiology of convulsions ap-

pears to be the *electroencephalogram*. Gibbs and Lennox³⁴ have demonstrated that improper cerebral rhythms are primary and that the epileptic paroxysm is only the superficial manifestation of an altered brain rhythm. In grand mal they find consistently fast rhythms, registering as spiked waves on the electroencephalographic tracing. In psychomotor epilepsy the rhythmic pace is slower, and the wave tracings blunted. In petit mal alternating fast and slow rhythms are noted. In a second study, Gibbs and Lennox³⁵ report that the electroencephalic patterns of dementia precox present a tracing of square waves not unlike the pattern in psychomotor epilepsy. This observation, compounded by the fact that insulin therapy is often helpful in petit mal, and by the statistically high proportion of epilepsy in schizophrenia suggest some affirmative relationship between the 2 disorders. For statistical support, they cite Jasper³⁶ who found epilepsy in 15 per cent of a group of schizophrenics. (Jasper and Solomon,³⁷ however, failed to find any consistent similarity in the electroencephalographic findings of epileptics and schizophrenics—EDITOR) Electroencephalograms are useful in pointing out not only the nature but also the site of the cerebral dysrhythmia. Jasper and Hawke³⁸ found that the anterior portion of the head was involved in half of their cases of grand mal. In petit mal, the posterior or parieto-occipital area was the commoner focus.

Standard air encephalography was found useful by Ruggeri³⁹ in distinguishing jacksonian from idiopathic paroxysms. He suggests that when encephalographic pictures are normal, the patient is likely to respond well to sedative treatment. In patients with roentgenologically visible brain lesions, notably in

those with enlarged ventricles, the prognosis is less favorable.

Symptomatology and Diagnosis—

The colloidal gold curve was found by Scheid⁴⁰ to be a useful means of distinguishing idiopathic from jacksonian epilepsy. It is almost never altered in true idiopathic convulsions, but usually shows abnormalities in the organic and jacksonian forms of the disorder. A *latent predilection* may be detected in persons who, with no frank epileptic symptoms, later develop grand mal. Gibbs and Lennox⁴¹ report that the cerebral dysrhythmia which is the fundamental basis of epilepsy can be observed electroencephalographically early in the course of the condition, long before the first grand mal convulsion. The importance of *allergic* phases of epilepsy is stressed by Clein,⁴² who records cases on an apparently allergic basis. These patients proved unresponsive to regular therapy. He suggests that a careful family history be secured, with especial attention to any record of migraine, hay fever, etc., and that skin and intradermal tests be performed on patients resistant to treatment.

Pederson⁴³ reminds us that, in the adult, convulsions are not uncommonly evidences of *brain tumor*. In meningioma, paroxysms occur in about one-third of the cases. A convulsion does not necessarily localize the tumor in the central motor region, though these reactions are commoner in neoplasms of the central and parietal areas than elsewhere in the brain.

Physicians are urged to chart carefully the day and time of each fit. Griffith and Fox⁴⁴ point out that untreated epileptics show a *predilection for the occurrence of fits at certain times of day*. In 1 series they found the greatest incidence between 6 and 7 A. M. If the diurnal rhythm and hour probabilities for a pa-

tient can be worked out by careful charting, patients can rebudget their schedules so as to be in nonhazardous places at the usual time of a convulsion. In this way the patient's fear of an accident may be reduced and the occupational schedules may be adjusted.

While epileptics frequently display personality oddities, these arise not so much out of the disease itself, as out of the patient's emotional and social response to his disorder. Barnes and Fetterman⁴⁵ find that the intelligence quotients of 101 clinic-attending epileptics range from 35 to 130 with a normal distribution, though the average I Q was only 74. Retesting indicated practically no fall in intelligence on the basis of the Stanford Revision of the Binet-Simon test, though with the Balcock test there was a fall in measured intellectual efficiency averaging 1 year between the 2 tests.

Treatment -- *Phenobarbital* is still the keystone of therapy in idiopathic epilepsy. Cohen and Myerson⁴⁶ found that phenobarbital could be made more effective by combining it with *benzedrine sulfate*. The dose of the latter is from 5 to 20 mg. a day. This reduces the drowsiness too often resulting from phenobarbital medication, and makes it possible to administer larger doses of the barbiturate. Another synergistic combination is suggested by Loscalzo,⁴⁷ who found *belladonna alkaloids* a valuable adjuvant. He prepares tablets each containing $\frac{1}{4}$ gram phenobarbital and $\frac{1}{250}$ gram of levorotatory belladonna alkaloids. Total dosage is from $\frac{1}{2}$ to 3 full tablets, 1 to 3 times a day. This was found more effective than uncompounded phenobarbital, and also more effective than a combination of bromides and phenobarbital.

Pollock,⁴⁸ however, still prefers bromides. In a group of 96 ambulatory epi-

leptics, he was able to effect prolonged remissions in 70 (73 per cent) by the use of *sodium bromide*.

Many drugs more effective than phenobarbital are known to biochemists, but few are clinically available. Merritt and Putnam⁴⁹ have found a series of phenone drugs, all of which were less soporific and more anticonvulsant. Included in their list were *aceto-phenone*, *benzo-phenone*, and *proprio-phenone*. Most potent, however, was *di-phenyl-hydantoin*, which, given intravenously, was found the most successful anticonvulsant in their series. The dosage of dilantin or di-phenyl-hydantoin is $1\frac{1}{2}$ grams 3 to 5 times a day. It is most effective in cases of major convulsions, but it is effective to a lesser degree in petit mal attacks. It has been reported as reducing very effectively the number of attacks during the day. *Ergotamine tartrate* is recommended by Rubenstone⁵⁰ for epileptics with low metabolic rates. His results, however, are not in accord with those of Loscalzo,⁵¹ who found this preparation of no value in controlling spells in any epileptic, regardless of metabolic rate.

For focal epilepsy, Furlow⁵² recommends *subpial resection*. Care should be taken to exclude brain tumor cases in classifying patients for this procedure. This operation, done under local anesthesia, requires a reflection of the dural flap over the presumably implicated area. The surgeon then stimulates with a unipolar electrode, applying the smallest amount of current which will produce slight contraction of the exposed temporal muscle. With this current, the affected area is demarcated by outlining the area which, when stimulated, reproduces the focal convulsive movements. The pia is then nicked, rolled back, and the underlying cortex spooned out. Furlow operated on 16 patients, had 2 deaths

(mortality $12\frac{1}{2}$ per cent) and 7 recoveries (recovery index 43 per cent). Most of the remaining 5 patients showed marked improvement, and all could return to work.

Narcolepsy—Irradiated ergosterol in a dosage of 10 drops, twice a day, was

found effective in preventing attacks in 2 cases of narcolepsy cited by Fessler.⁵³ Abstinence from alcohol also reduces attack incidence. During ergosterol administration, it is advisable to keep serum calcium content under careful supervision.

MENINGITIS

By HENRY A. DAVIDSON, M.D.

Meningococcic and Streptococcic Meningitis

Prevention—Immunization of human beings against meningococcic meningitis is a reasonable possibility, if Kolmer's experiments⁵⁴ on protective vaccination of laboratory animals can be extended to the clinical field. Kolmer cultured the vaccine in hormone broth and sterilized with tricresol. Subsequent intracisternal inoculation of the animals produced fatal meningitis in half of the immunized rabbits, in all of the unprotected subjects. An actual clinical experiment in meningitis immunization is reported by Kuhns⁵⁵ and his coworkers. They used the soluble toxin in the filtrate from meningococcus broth culture. Full strength filtrate was given subcutaneously in 0.2, 0.5, and 1.5 cc amounts at 4-day intervals to enrollees in a C. C. C. camp. Three untreated campers developed meningitis, none of the immunized subjects in the same camp were affected. Kuhns warns that in immunizing newly concentrated groups in the presence of impending epidemics, it is best to inoculate all subjects rather than to depend on intradermal testing to differentiate immune and susceptible persons.

In a case of brain abscess with a threatened streptococcic meningitis, Bucy⁵⁶ was able to prevent the meningitis and cure the abscess by *sulfanilamide* ad-

ministration. In his patient, streptococcic cerebellar abscess was confirmed by culture of the pus obtained by aspiration. The abscess was not drained, but suboccipital decompression was done. The adjacent ventricles and subarachnoid spaces swarmed with the streptococci. Sulfanilamide tablets (5 grains—0.3 Gm—each) were given daily by mouth. Bucy points out that the single aspiration could not have cured the abscess nor prevented the impending meningitis. Prevention of the latter complication was considered the result of the sulfanilamide administration.

Prognosis — Streptococcic Meningitis—Prior to the use of sulfanilamide, the mortality from streptococcic meningitis was practically 100 per cent. With intensive sulfanilamide therapy, however, a high percentage of recovery is possible. Eley,⁵⁷ indeed, reported no mortality (6 recoveries in 6 cases). The highest fatality record with sulfanilamide is that of Silverthorne and Brown,⁵⁸ who effected 5 recoveries in 9 cases (44 per cent mortality). Neal⁵⁹ records a 20 per cent recovery rate in one series, and, with Applebaum,⁶⁰ a fatality ratio of only 11 per cent in another series.

Meningococcic Meningitis—Walsh's⁶¹ figures show a meningitis mortality rate varying from 69 to 76 per cent prior to the use of serum. With

serum, he found that death rates averaged about 50 per cent. With sulfanilamide, however, the highest mortality—reported by Eldahl⁶²—was 25 per cent. Muraz and his associates⁶³ reduced the mortality to only 8 per cent, combining *serum* and *sulfanilamide* therapy. The most favorable report, that of Banks,⁶⁴ shows 15 recoveries in 16 cases treated by sulfanilamide alone. This is a fatality rate of only 6 per cent.

Blood Stream Infection—A blood stream infection complicating a meningococcal meningitis indicates its presence, according to Craster and Simon,⁶⁵ by a specific petechial rash. This is an early finding, occurring even before spinal fluid becomes cloudy. Blood removed from a petechia by needle puncture often shows the cocci with Gram's stain.

Treatment—Sulfanilamide—As reviewed above (see PROGNOSIS), sulfanilamide has changed the prognosis of streptococcal and meningococcal meningitis from grave to favorable. This medication may be given directly, or in the form of *prontosil*. A 2.5 per cent prontosil solution will yield $\frac{1}{10}$ gram (0.007 Gm.) of sulfanilamide per cc.

Sulfanilamide may be administered as follows:

By Mouth—Tablets, 5 grams (0.3 Gm.) or 10 grams (0.6 Gm.)

Intraciously—Hypotonic saline containing 0.375 per cent sulfanilamide

Intramuscularly—Sulfanilamide, 0.8 per cent solution

Intraspinally—Sulfanilamide, 0.8 per cent solution

Prontosil may be administered as follows:

By Mouth—By a 2.5 per cent solution, 50 cc. yields 5 grams of sulfanilamide

Intramuscularly—In 10 to 15 cc. doses

Intraspinally—In 5 to 20 cc. doses, depending on the quantity of spinal fluid removed.

In *streptococcal meningitis*, Silverthorne and Brown⁵⁸ recommend the

following régime: (a) *Continuous intravenous injection of dextrose-saline*; (b) *daily spinal drainages*, and (c) *sulfanilamide* by mouth. Neal and Applebaum⁶⁰ use 10 cc. of *prontosil* intramuscularly every 4 hours or 10 grains of sulfanilamide by mouth every 6 hours. Smith and his colleagues⁶⁶ report recovery in a severe case of anaerobic beta-hemolytic streptococcal meningitis of otitic origin effected by the use of 15 cc. of prontosil intramuscularly every 8 hours for 3 days, followed by the oral administration of 10 grains of sulfanilamide every 4 hours for 2 weeks. Neal⁵⁹ suggests oral medication unless the patient cannot swallow. She combines 10 cc. of prontosil every 4 hours (by mouth) with 5 to 15 grams of sulfanilamide every 6 hours. The dosage for children is correspondingly reduced. Intraspinal or intramuscular injection should be reserved for comatose patients.

For *meningococcal meningitis*, Banks⁶⁴ prefers high initial doses to maintain the sulfanilamide level in the spinal fluid at 5 mg. per 100 cc. for at least 3 days. Eldahl⁶⁷ finds injections better than oral medication. He uses the 0.8 per cent sulfanilamide solution, the daily intramuscular dosage total varying from 35 to 150 cc., depending on the patient's weight. This he combines with the intraspinal use of the same medication, the daily intrathecal intake falling between 5 and 30 cc., depending on the amount of spinal fluid removed. Muraz⁶³ has seen gratifying results with the 5-grain sulfanilamide tablets. He starts with 4 tablets, 4 times a day and halves the dosage after the second day. In his average case, each adult ingested a total of about 100 tablets before it appeared safe to discontinue medication. He urges the simultaneous use of serum with the sulfanilamide. Retan⁶⁸ recommends intravenous injection of 0.375 per cent

sulfanilamide solution in hypotonic saline. The injection rate should approximate 10 cc. per hour per pound of body weight. The total daily sulfanilamide intake by this method should approximate 100 or 200 grains (6 to 12 Gm.) a day. During injection, spinal tap relieves intracranial pressure and favors passage of the drug across the hematoencephalic barrier. Osgood⁶⁹ reports that he finds smaller doses of sulfanilamide at frequent intervals more effective than larger doses at longer intervals.

To avoid toxic effects, Alpert and Forbes⁷⁰ suggest the daily determination of the sulfanilamide blood content, hemoglobin proportion and leukocyte count.

Acriflavine—In a severe case of meningococcic meningitis, Puig⁷¹ effected cure by a single intraspinal injection of 7 cc. of a 1:20,000 solution of acriflavine, combined with daily intravenous injections of 1:200 acriflavine solution.

Therapeutic Spinal Drainage—Continuous subarachnoid drainage was successful in treatment of 28 cases of meningococcic meningitis reported by Thompson⁷². A special self-retaining screw cannula is used. The fluid is connected with a manometer, adjusted 10 inches above the patient's head. Thompson warns not to insert the drainage tap until fluid pressure has been reduced to 100 mm. Leave the trocar in position to allow gradual pressure reduction. When the flow ceases, the manometer is lowered in stages until the final position allows for 100 mm. of intrathecal pressure. Such a technic provides for continuous escape of meningeal exudate, avoids spinal blocks and eliminates traumata of repeated taps.

Staphylococcic Meningitis

Staphylococcic meningitis is rare. Recovery from this form of infection is also rare. A case successfully treated by

sulfanilamide is cited by Bloch and Paccella.⁷³ Their patient was only 17 days old. He was born with an occipital meningocele. After it had been removed, an occipital protrusion remained. When the child developed convulsions, the scab over the protrusion was removed, exposing a layer of pus laden with staphylococci. Intrathecal sulfanilamide was given for 8 days and oral sulfanilamide for 27 days. The infant recovered.

Pneumococcic Meningitis

Reviewing 99 cases of pneumococcic meningitis, Finland and his associates⁷⁴ find that 10 received sulfanilamide and 89 did not. The mortality rate was 40 per cent in the sulfanilamide-treated group, and 100 per cent in the series of patients not receiving sulfanilamide. The recommended procedure is as follows: (a) **Complete, frequent spinal drainage**, (b) large doses of **sulfanilamide**, by mouth or subcutaneously, (c) intravenous administration of the **specific pneumococcus serum**, and (d) intraspinal injection of 5 to 10 cc. of the **patient's own blood serum**. Recovery from a case of type VII pneumococcic meningitis is reported by Querv.⁷⁵ In this case, sputum showed the pneumococci. The spinal fluid culture was also positive for type VII pneumococcus. Treatment consisted in the oral administration of sulfanilamide in large doses. On the fifth day, the patient became comatose and it was necessary to give the medication subcutaneously. At the same time the specific serum was given intravenously and intrathecally. Recovery was complete.

Actinomycotic Meningitis

Only 110 cases of actinomycosis of the central nervous system have been reported. To this meager list, Morrison, Humphrey and Bailey⁷⁶ add a case of

actinomycotic meningitis following a primary focus in a finger. A 12-year-old boy had a painless finger lesion, from which thick brown pus was obtained on incision. Two weeks later he developed headache, stiff neck and vomiting. Both optic nerve heads were choked. The spinal fluid was turbid, and the cell count varied from 2600 to 7100. Smear of the finger discharge showed the fungus with typical rays and clubbed borders indicative of actinomyces. The child died. Necropsy revealed flattening of the cerebral convolutions with a thick exudate covering the base of the brain. The abscess had ruptured into the ventricle, from which mycelial filaments could be recovered.

Gonococcic Meningitis

Though infrequently reported, gonococcic meningitis probably is more common than suggested by the scanty records. Casual microscopic study of the spinal fluid is inadequate to differentiate the meningococcus from the gonococcus. Consequently many cases of Neisserian meningitis are classed as cerebrospinal fever. During the last few years, Washington's National Health Institute has received for cultural classification 500 specimens labelled "meningococcus." In 10 cases the organism was actually identified as gonococcus (Branham, *et al*⁷⁷).

Clinically, gonococcic meningitis may be a complication or sequel of urogenital gonorrhea; or a neonatal infection; or, in some instances, a primary meningitis without any known mucous membrane focus. A case of the latter is cited by Branham, Mitchell and Brainin.⁷⁷ Their patient, a 16-year-old virgin, developed headache, vomiting, and stiff neck. Vaginal smears were negative, but gonococci were identified in the cloudy spinal fluid. The patient made a rapid recovery on

sulfanilamide. For the first 3 days she received 20 grains (0.13 Gm.) every 4 hours; the dosage was gradually reduced, reaching 10 grains (0.6 Gm.) 4 times daily on the tenth day. Daily intraspinal injection of 30 cc. of aqueous solution, 1 per cent, sulfanilamide were also administered during the first 4 days.

In contrast to this case, in which no primary gonorrhea was found, is the report cited by Marvin and Wilkinson⁷⁸ of acute urethral gonorrhea complicated by a meningitis. Their patient, an 18-year-old boy, had a profuse, gonococcus-laden, urethral discharge. Nine days later, while under treatment for the urethritis, he complained of headache, vomiting, and stiff neck. The cloudy spinal fluid contained gram-negative diplococci. Agglutination tests with a recently recovered gonorrheal urethritis case were positive. Treatment consisted of the oral administration of 5 grains (0.3 Gm.) of sulfanilamide 3 or 4 times a day. Recovery was complete.

Identification of the gonococcal nature of the meningitis is important to avoid traumatizing with futile serum therapy. Points of differentiation between the gonococcus and meningococcus are listed by Branham, Mitchell and Brann.⁷⁷ Cultured colonies of gonococcus are delicately growing, small and translucent. The meningococcus colony is more luxuriant in growth, larger in size. Gonococci will ferment dextrose, but no other sugars. Meningococci rarely ferment dextrose alone. Gonococcal culture suspensions dissolve completely in Thomson's alkaline medium, meningococci do not. For differential growth, Bailey⁷⁹ has prepared a medium consisting of whole serum from which diastase and other fermentable substances have been removed. A concentrated broth containing inorganic salts and carbohydrate is

added to the medium. Differentiation between meningococci and gonococci can be established on this medium within 24 hours.

Serous or Lymphocytic Meningitis

The special virus supposed to cause lymphocytic choriomeningitis is not responsible for all cases which conform to this clinical picture. Baird and Rivers⁸⁰ report that the virus-caused lymphocytic meningitis may be distinguished from clinically identical forms of different origin by the fact that the spinal fluid cell count is higher in cases caused by the Wallgren virus. Some cases, apparently belonging to the class of lymphocytic meningitides, are really preparalytic stages of poliomyelitis, Fanconi⁸¹ warns. He suggests that careful motor examination for localized evidence of muscle weakness, and finding of depressed tendon reflexes, should point to the possibility of an abortive or preparalytic poliomyelitis in cases otherwise conforming to the picture of serous meningitis. The term "benign" applied to lymphocytic meningitis may be a misnomer, as indicated by a fatal case reported by Martinetti and Carere-Comes.⁸² Their patient, a 15-year-old boy, had an attack of headache and stiff neck with a laboratory picture consistent with serous meningitis. He recovered in a few months, only to be stricken several weeks later with violent headache and vomiting. He died 2 weeks after the onset, and necropsy revealed a marked internal hydrocephalus presumably due to inflammatory hypersecretion of spinal fluid.

The importance of trauma in provoking serous meningitis is stressed by Puech and Krebs,⁸³ who prefer to think of the condition as a "traumatic arachnitis." In these cases, they report favorable results after surgical evacuation of the pools of fluid.

For ordinary cases of serous meningitis, Molhant⁸⁴ recommends the following treatment program: (a) *Hypertonic infusions of dextrose*; (b) *intradermal tuberculin desensitization*; (c) repeated *lumbar punctures*, and (d) *roentgenotherapy*. The latter reduces secretion of fluid, while the tuberculin injections desensitize the organism.

Tuberculous Meningitis

To distinguish tuberculous meningitis due to the bovine bacillus from the form due to the human tubercle bacillus, Lesne and Saenz⁸⁵ use Loewenstein's medium. They find that in the latter type, the appearance of colonies required from 11 to 29 days. The colonies were reddish, dry, abundant, and averaged 8 mm in diameter. The bovine bacillus colonies were smaller, moister and colorless. The younger children (under 5 or 6 years of age) were more likely to be afflicted by the bovine, the older by the human organism. The bovine form is commoner in rural areas and the human form in urban zones. Raw cow's milk is the source of the bovine infection, personal contacts of the human. According to Nobecourt and Briskas,⁸⁶ tuberculous meningitis as a complication of tuberculosis develops most commonly in the spring or summer. The interval between the beginning of the tuberculous infection and first meningitic manifestation was very variable, 3 to 20 weeks. Investigating the neuropathologic features of tuberculous meningitis, Beres and Meltzer⁸⁷ found an extension of the inflammatory process into the cortex resulting in foci of encephalitis. The tubercles were seldom found in great numbers except when there was blood stream dissemination. In a few cases, they discovered a cortical tubercle pre-existing the meningitis, and apparently responsible for it.

Test for Tuberculous Meningitis

—For the early recognition of the tuberculous nature of a meningitis, Guglielmini⁸⁸ recommends the tryptophan test, performed as follows: Mix 3 cc. of spinal fluid with 15 cc. of concentrated hydrochloric acid. Add 3 drops of a formalde-

hyde (2 per cent) solution. Over this mixture stratify 2 or 3 cc. of a 0.06 per cent solution of sodium nitrite. If tryptophan is present, a violet ring will appear at the point of contact between the 2 fluid layers. Occurring within 3 minutes it indicates a tuberculous meningitis.

MIGRAINE

By ELI MARCOVITZ, M.D.

Very little progress has been made in the treatment of migraine. Ergotamine tartrate continues to be the most efficacious treatment in most cases.

Mechanism—J. R. Graham and H. G. Wolff⁸⁹ found that changes in the intensity of the migraine headache are closely related to changes in the amplitude of pulsations of branches of the external carotid arteries. Factors which decreased the amplitude of the pulsations (e.g., manual pressure on the common carotid artery) were accompanied by reduction in the intensity of the headache. On the other hand, distention of the temporal artery by experimental increase of the intramural hydrostatic pressure produced pain. Ergotamine tartrate, while diminishing the intensity of the headache, reduced the amplitude of the pulsation by approximately 50 per cent. The authors conclude that their results support the view that the head pain of the migraine attack is produced by distention of the cranial arteries and that the termination of the headache by ergotamine tartrate is due to the capacity of this agent to constrict the cranial arteries and thus reduce the amplitude of the pulsations.

Etiology—Various factors continue to be regarded as important in the etiology of migraine. P. Matzdorff⁹⁰ reports 12 cases of migraine following

cranial trauma. He insists that "adequate" trauma is necessary before it can be considered an etiologic factor. Mild cranial trauma is deemed insufficient to account for migraine headache.

The same author⁹¹ cites cases in which fever, infections, and syphilis seem to play a part in the etiology.

C. L. Hartsock and F. J. McGurl⁹² believe that allergic phenomena are the etiologic factors in most cases of migraine. They state that 75 per cent of cases are helped by allergic treatment, 30 per cent completely and 45 per cent partially. Only 25 per cent, according to their findings, are not helped by these means. They believe that in states of fatigue or emotional upset hyperperistalsis occurs, with consequent stasis or reverse peristalsis. This creates a condition favorable for the absorption of whole protein molecules, which is probably necessary in order to produce a reaction in the shock organ. They add that with ergotamine tartrate headaches are only allayed, and that attacks come at more frequent intervals, so that little is gained by ergotamine treatment.

Occurrence in Children—H. A. Riley⁹³ discusses the occurrence of migraine in children, and points out that when migraine occurs in early life it usually is the ophthalmic type and is frequently accompanied by gastrointestinal

symptoms. In many cases the gastrointestinal disturbances may replace the headache (migraine equivalent). He advises that when children present repeated gastrointestinal episodes, inquiries should be made into the occurrence of migraine in the family. He has found that cyclic vomiting in children is often replaced by migraine in later life. He also notes that migraine in children tends to disappear at the onset of puberty, only to recur frequently at the menopause.

Treatment—W. G. Lennox⁹⁴ compared the action of ergonovine, a newly isolated alkaloid of ergot, with that of ergotamine in patients with migraine. He found that by oral administration *ergonovine* was about as effective as *ergotamine*. Parenterally, however, it was only about half as effective in reducing headache, but was accompanied by less than half as many attacks of vomiting. There is no correlation between the relief of headache and vomiting. The author has found that when a patient who is usually relieved by ergotamine has a very severe attack which does not respond to treatment then an additional injection of 2 cc of *cibalgin* (an amidopyrine preparation) will promptly bring relief.

He advises that if ergonovine proves to be effective in any case, it should be

used in preference to ergotamine. It should not be used in pregnancy because its action as an abortifacient is stronger than that of ergotamine.

The termination of headaches by ergot alkaloids cannot be explained by the accompanying circulatory changes, for similar or even greater changes in blood pressure, blood flow, blood concentration and heart rate can be brought about by other agencies which do not stop migraine headaches. Neither do the ergot alkaloids act by a paralyzing action on the sympathetic nervous system to produce dilatation of spastic cerebral vessels, nor by the anesthetizing of pain-carrying sensory fibers. Their action seems to be one of stimulation, causing a "tightening up" of the vascular system.

The effective component in these ergot alkaloids is not the oxytocic principle, but the fraction which causes contraction of the arteries and depression of the heart rate.

To prevent the occurrence of nausea, vomiting and muscular cramps which frequently accompany the administration of ergotamine, M. E. O'Sullivan and V. T. Raybin⁹⁵ recommend the use of calcium gluconate and vitamin D between attacks. At the time of the attack also, intravenous calcium gluconate may be used in conjunction with the administration of ergotamine tartrate.

MULTIPLE SCLEROSIS

By ELI MARCOVITZ, M.D.

There have been no fundamental contributions to our knowledge of the etiology or to the treatment of multiple sclerosis during the past year.

Pathology—Continuing his studies on the vascular background of the lesions of multiple sclerosis, T. J. Putnam,

with A. Adler⁹⁶ made glass plate reconstructions of plaques occurring in multiple sclerosis. They conclude that the vascular architecture of the lesions of multiple sclerosis is characteristic. Small plaques tend to surround engorged veins, which are gnarled and tortuous

If a thrombus occurs in a vein, an area of fresh degeneration appears in close relation to it. There is usually an increase of capillaries in sclerotic plaques, but a decrease may also be found.

On the other hand, G. B. Hassin⁹⁷ insists that in multiple sclerosis the changes in the myelin are primary, and that these changes occur as a direct result of some toxic process. He denies that vascular changes, *e g.*, venous thrombosis, have any primary influence on the production of the myelin changes.

Pathogenesis—In view of the studies which have tended to show that in multiple sclerosis there is an abnormal lipolytic activity in the blood serum due to an increased lipase content, K. C. Swan and H. B. Myers⁹⁸ made repeated lipase determinations over a period of 18 months on the serums of 9 patients with multiple sclerosis. In only 1 case was there definite evidence of lipolytic activity in the serum, and this was absent in a later determination. This case was the only one which had not shown clinical evidence of progression of the disease within 1 year of the determinations. Their studies reveal no substantial evidence to support the concept that abnormal lipolytic activity of the serum is present in multiple sclerosis.

Clinical Pathology—S. M. Dilenberg⁹⁹ compared the spinal fluid findings (cell count, globulin, total protein and gold curve) in clinically active and inactive cases of multiple sclerosis. He found that active cases tended to show slight abnormalities in these features more frequently than inactive cases.

Treatment—G. Schaltenbrand¹⁰⁰ has obtained his best results in multiple sclerosis by means of *diets high in raw food and in content of vitamins A, B, C, and D*. In discussing prognosis he states that an earlier onset indicates a better prognosis for life, whereas a later onset is usually accompanied by a more rapid course.

R. M. Brickner and D. J. Simons¹⁰¹ report on the use of *ergotamine tartrate* and *benzedrine sulfate* in multiple sclerosis. They found that some patients showed a diminution of spasticity during a few hours following the administration of ergotamine parenterally and orally. Sometimes this was of practical value. Benzedrine was more commonly effective. More than half of the cases reported an increase in strength and a relaxation of spasticity, while one-third noted improvement of the intention tremor, following the use of benzedrine. The authors recommend a trial of each of these drugs in multiple sclerosis.

MYASTHENIA GRAVIS

By ELI MARCOVITZ, M.D.

Although reliance is still placed on prostigmin in the treatment of myasthenia gravis, it has been found that in many cases it loses its efficacy, and that increasing the dosage may produce unfavorable results. Numerous studies have been reported on the choline-esterase content of the blood of myasthenics in

an effort to clarify the pathophysiology underlying this disease. Contrary to the theory that the symptoms are due to a more rapid destruction of acetylcholine at the myoneural junction by increased esterase activity, most investigators agree that the difficulty is more likely in the impairment of the production or

utilization of acetylcholine. Prostigmin acts to impede the destruction of acetylcholine by the choline esterase.

Pathophysiology—F. R. Fraser, M. McGeorge, and G. E. Murphy¹⁰² used *carbaminoyl choline chloride*, *acetyl choline chloride* and *acetyl B-methyl choline chloride (mexolin)* by subcutaneous injection in cases of myasthenia gravis. They found that these choline compounds produced a response similar to that of prostigmin, except that the response was much slower and also much more prolonged. Choline itself had no effect. From these studies the authors conclude that the choline esters are utilized in the elaboration of a precursor from which acetylcholine is set free at the myoneural junction, and that a defect in the production of acetylcholine is present in myasthenia gravis.

T. Stedman and W. R. Russell¹⁰³ found no increase over the normal in the amount of choline esterase in the blood of patients with myasthenia gravis. They conclude, therefore, that the weakness of this disease is due to a deficiency in the production of acetylcholine in nervous tissue, or to a defect in the mechanism of its liberation. The authors hypothesize that the body attempts to compensate for this by decreasing the amount of choline esterase in the blood serum, and later even in the blood corpuscles and tissues. They believe that this state is accompanied by a remission of symptoms.

A. B. Corkill and A. H. Ennor¹⁰⁴ report that marked variations in choline esterase occur in normals and in patients with various medical conditions. They found no correlation between the amount of esterase and the clinical condition of the patient. They also feel, therefore, that weakness does not depend on increased esterase activity, but that there

must be a deficiency in the production of acetylcholine.

Contrary to the findings of these investigators, however, C. S. Hicks and M. E. Mackay¹⁰⁵ found evidence of consistently higher choline esterase activity in sera from the blood of cases of myasthenia gravis than in sera from normal subjects. Also, sera from cases of myotonia congenita showed consistently lower choline esterase activity than the lower limits of normal sera.

As part of their work on creatine metabolism (see section on Myopathies) A. T. Milhorat and H. G. Wolff¹⁰⁶ studied patients with myasthenia gravis. In this condition they found only a slight abnormality in creatine metabolism except possibly just before death, when there occurred some excretion of creatine in the urine and a diminution of creatine tolerance (the ability to retain ingested creatine). The metabolism of creatine is normal during remissions, but is usually abnormal during exacerbations. The metabolism disturbances may vary with the degree of impairment of muscular function, but they do not precede the onset of exacerbations. They make their appearance after an obvious increase in weakness. Where creatine metabolism is abnormal during exacerbations, improvement by prostigmin or ephedrine is not necessarily associated with a return of the creatine metabolism to a normal state. Furthermore, when the creatine metabolism remains abnormal despite improvement under treatment with prostigmin or ephedrine, the improvement is only temporary. The authors conclude that the fundamental metabolic disturbance in myasthenia gravis is not centered in the metabolism of creatine and creatinine, but that the metabolism of creatine is involved secondarily when the abnormal process has become severe. Moreover, once these

metabolic processes are seriously involved, the prognosis for life is grave.

Treatment—J. L. Robinson¹⁰⁷ reports a case of myasthenia gravis in which, in spite of treatment with *prostigmin* and *ephedrine*, the patient became progressively worse, and finally moribund. He then administered *insulin*, 5 units 3 times daily, plus 3 tablets and 1 ampule of prostigmin daily. There ensued a remarkable improvement; the patient was up in a few days, and in 2 weeks had resumed her normal duties. At the time of the report, 2½ months after the start of insulin

treatment, she was still well, and was receiving 5 units of insulin twice daily, and 1 tablet of prostigmin 3 times daily.

Foster Kennedy and Alexander Wolf¹⁰⁸ were able to restore 5 patients with myasthenia to normal activity with the use of prostigmin, 4 other cases, however, after early improvement, showed a progression of symptoms in spite of increase of dosage. In fact, increasing the dosage seemed to aggravate the myasthenic weakness, which sometimes improved on reduction of the dose. They found that quinine aggravated the weakness of myasthenia.

MYOPATHIES

By ELI MARCOVITZ, M.D.

There has been little progress in the treatment of the myopathies during the past year. In *myotonia*, *quinine* proves efficacious in most cases. In the *muscular dystrophies*, *glycocoll* (amino-acetic acid) is still used, for want of any more specific treatment.

The most important contributions to our knowledge of the myopathies have come from the studies of A. T. Milhorat and H. G. Wolf¹⁰⁹ on the metabolism of creatine and creatinine in various diseases which involve the muscles.

Normally creatinine is excreted in the urine in amounts varying directly with the state of development of the skeletal musculature; in other words, creatinine excretion is proportional to the muscular mass. In patients with muscular disease the amount of creatinine in the urine is diminished. In these states the creatinine output appears to be an expression, not of the amount of muscle *per se*, but of the amount of efficiently functioning muscle tissue.

Creatinuria is not present in well-muscled adult males. Creatine appears in small amounts in the urine of adult females, and in larger amounts in the urine of children. The creatine tolerance is a measure of the ability of the body to retain ingested creatine. Normally nearly the entire ingested amount is retained. In diseases affecting muscles, creatine appears in the urine, even when the patients are maintained on a creatine-free diet. This is usually accompanied by a diminution of creatine tolerance.

In progressive muscular dystrophy large amounts of creatine are often excreted. The level of creatine in the urine and the impairment of creatine tolerance are related to the amount of muscular disability. In advanced stages of the disease the entire ingested dose of creatine may be excreted in the urine as creatine.

When amino-acetic acid is ingested for short periods of time it appears to amplify the defects in creatine tolerance. These effects differ from the results of

prolonged injection of amino-acetic acid. The effects noted are out of all proportion to the effects of comparable amounts of nitrogen.

In patients with muscular wasting the total creatine coefficient (mg. of creatine and creatinine per kg of body weight) diminishes as the incapacity of the muscle advances.

The authors conclude that the creatine output and creatine tolerance appear to be an expression of the total mass of improperly functioning muscle, and not, *per se*, an index of the amount of wasted muscle or the primary site of the disease.

The authors also investigated patients with Charcot - Marie - Tooth peroneal muscular atrophy, and patients with muscular involvement subsequent to peripheral neuritis, anterior poliomyelitis, amyotrophic lateral sclerosis and so-called neuronitis. In these cases they found that in the presence of muscular wasting the diminution in the output of creatinine appears to be directly proportional to the reduction in muscle mass. The amounts of creatine eliminated are smaller than are observed in patients with progressive muscular dystrophy with similar amounts of apparent muscular wasting. Also the impairment in creatine tolerance is less than in similarly incapacitated patients with progressive muscular dystrophy, and the administration of amino-acetic acid is without effect on the output of creatine or on the creatine tolerance unless there is extensive wasting. However, when the muscular involvement is so extensive as to include most of the skeletal musculature, then defects in the metabolism of creatine and creatinine may equal those seen in the advanced stages of progressive muscular dystrophy. Apparently as long as a large portion of the striated musculature remains intact the ability to retain ingested creatine is little affected

In contrast to these processes characterized by decrease in muscular function, the authors also studied cases showing a pathological increase in muscular activity, *viz.*, myotonia congenita and atrophica, dystonia musculorum deformans, and paralysis agitans. In myotonia congenita, dystonia and paralysis agitans there was no abnormality in creatine metabolism.

In myotonia atrophica, where wasting occurs, abnormalities were found, *e. g.*, a diminution in the excretion of creatinine directly proportional to the reduction in muscle mass. However, in mild and moderate cases, creatinuria and reduction of creatine tolerance were only of a moderate degree, less than in cases of progressive muscular dystrophy with similar muscular disability, and the ingestion of amino-acetic acid did not affect the creatine tolerance. In cases with extreme involvement, large amounts of creatine were excreted, the creatine tolerance was seriously impaired, and ingestion of amino-acetic acid caused an increase in the output of creatine and a further decrease in tolerance.

In short, the authors found that patients with myotonia atrophica resemble more closely patients with muscular wasting subsequent to disease of the nervous system than those with progressive muscular dystrophy. But they stress that these findings do not justify any inference regarding the primary site of the disease in myotonia atrophica. They also note that in amyotonia congenita the defects in creatine metabolism closely resemble those occurring in progressive muscular dystrophy.

Clinical Observations—O. Maas¹¹⁰ studied 57 families (5 were Jewish, the rest British or German) in which 1 or more members were affected with dystrophia myotonica (myotonia atrophica).

He made a number of important observations. Severe symptoms occur more frequently in the males, mild and suspicious symptoms more frequently in the females, but it is probable that numerically the sexes are equally affected. The myotonic reaction is found more often on mechanical stimulation than on active movements, and all striated muscle may exhibit the reaction. Cases differ with regard to the severity and the location of muscular wasting. Weakness may occur without definite wasting. Hypertrophy or "pseudohypertrophy" occurs but rarely. In all his cases, not one was an instance of pure Thomsen's disease (myotonia congenita). Four cases had been so diagnosed, but these were found to have a few wasted muscles or early cataracts. The sex glands were found to be atrophied in most cases, although in 2 cases of severe atrophy function was apparently preserved.

In many supposedly healthy relatives suspicious myotonic reactions or suspicious wasting of muscles or suspicious lens alterations were observed.

The disease often begins in early childhood. In families in which 1 definite case occurred nearly all the othersiblings showed either definite or more or less suspicious signs of the disease. The younger siblings were often severely affected, especially the youngest male. The younger members tend to become affected at progressively earlier ages. The disease often affects members of succeeding generations, and seems to be transmitted as a dominant characteristic. However, more than 1 genetic factor may be involved. It may be transmitted by persons unaffected with signs of the disease. In succeeding generations there is a ten-

dency to progressive physical and mental deterioration.

Treatment—L. C. Kolb, A. M. Harvey and M. R. Whitehill¹¹¹ report on 8 cases of myotonia atrophica and 1 of myotonia congenita. They found that *quinine* abolished myotonus but had no effect on muscular strength. Prostigmin increased the myotonus and directly antagonized the full therapeutic effect of quinine. Parathyroid extract, potassium chloride and adrenal cortical extract all failed to reduce myotonus.

Parathyroid extract and **adrenal cortex** have been used by L. Berman¹¹² in progressive muscular dystrophy with apparently good effect. On the theory that the parathyroid and the adrenal cortex hormones were most definitely involved in the disturbance of sugar and phosphocreatine metabolism in this disease, the author administered these hormones in 22 cases. Fifteen showed marked improvement with a rise in blood sugar and blood cholesterol, normalization of the blood sugar tolerance curve, reduction in creatinuria and an increase in creatine tolerance.

L. F. Bender¹¹³ reports good results with *glycocoll* in retarding the progress of pseudohypertrophic progressive muscular dystrophy. The dosage recommended is 5 Gm. twice daily for children under 10 years, and 5 Gm. 3 times daily for children over 10 years. He also recommends *glycocoll electrophoresis*. In the latter procedure he advises the addition of *mecholy* to the glycocoll solution. Mecholy acts as a vasodilator and helps the absorption of glycocoll into the tissues. A further refinement is the use of *imadyl inunction* with vigorous massage to the part to be used for iontophoresis.

TUMORS OF THE BRAIN

By ROBERT A. GROFF, M.D.

Diagnosis—Aids to the clinician in making an early diagnosis from the historical data of a patient developing a brain tumor is given by F. M. R. Walshe¹¹⁴ This writer states that the clinical course of an intracranial tumor is likely to follow 1 of 4 main lines of development.

The first is characterized by the recurrence of generalized epileptic fits. When such convulsions make their appearance in a middle-aged person they should give rise to suspicion of tumor. Jacksonian fits may also occur as an early sign of tumor of the brain, but are less common.

The second and most common mode of onset is that in which there develops signs and symptoms of increased intracranial pressure: namely, headache, vomiting and papilledema (choked discs). The headache is characterized in most instances by awakening the patient in the early morning hours and is most severe during this time. The pulse may be slow, a not infrequent sign except in the patient with a rapidly growing glioma. A high degree of papilledema may exist with normal vision.

The third mode of evolution is that in which there is evidence of a progressive local lesion. Slowly developing weakness of one side of the body is an example. Walshe states, however, that paralysis agitans without tremor may give a similar picture and mentions 2 cases in which the patient was subjected to a craniotomy.

The fourth mode of onset described by Walshe is seen in patients who develop metastatic carcinomatous lesions of the brain. These lesions, usually multiple, may produce marked disturbances

characterized by muttering, delirium, gross defect of memory and confusion. Meningeal involvement by metastasis may produce signs which are suggestive of meningitis. Carcinoma cells have been found in the spinal fluid on rare occasions.

The suspicion of a diagnosis of brain tumor having been aroused, the next problem to consider is: Is there a tumor? Where is it located? What is its probable nature? These questions are answered by Dott.¹¹⁵ According to this writer, the histological character of the tumor and the exact boundaries of the lesion are just as important as the diagnosis of an intracranial growth. The examinations which help us in answering these 3 questions are:

Roentgenography—This study may give very valuable information. Calcification in the tumor may be demonstrated, erosions or hyperostosis of the skull and erosions of the foramina of the cranial nerves may be visualized. Calcification in the pituitary and pineal gland permit recognition of a shift of the structures from their midline position. Widening of the suture lines, decalcification of the choroid processes and accentuation of the digital markings are signs of increased intracranial pressure.

Lumbar Puncture—According to Dott the danger of this procedure in cases of increased intracranial pressure is greatly overemphasized. If it is done by a competent neurologist, valuable information may be obtained.

Ventriculography—This is necessary in about 40 per cent of patients in whom a diagnosis of a mass lesion within the skull has been made, according to Dott. He states that this diagnostic test should

be followed immediately by a craniotomy or craniectomy, depending upon the location of the lesion.

Encephalography—This is employed only to supplement a ventricular injection of gas which has inadequately filled the ventricles.

Cerebrovascular Roentgenography—This is also advocated. Colloidal thorium dioxide is injected into the exposed internal carotid artery. The arterial displacements around the tumor may give exact information as to its extent. This method is of special value in patients in whom aneurism is suspected.

Biopsy—This may be utilized according to Dott by means of a trephine with an exploring cannula over the lesion. This procedure may be performed when a glioblastoma, the most malignant type of glioma, is suspected. Operation in these patients does offer much in the relief of symptoms and the prolongation of life. For this reason, operation is usually undesirable.

If the clinical examination is supplemented by one or more of these special procedures, a correct diagnosis of tumor and its location can be made in 99 per cent of cases, according to Dott. The histological nature of the tumor can be forecasted with reasonable certainty in 70 per cent of cases.

Value of Signs—Certain signs have been ascribed to a particular part of the brain when that part is involved by a lesion, especially one of vascular origin. Brain tumors, on the other hand, not only cause a destruction of the area in which they grow but usually add to the picture the effects of increased intracranial pressure. The natural question that arises is: Are the signs presented by tumors of the brain reliable aids in localization, and which are the most trustworthy?

Bamford¹¹⁶ has attempted to answer this question by studying the signs in a series of 306 verified cases, 56 of which were midline tumors. The accuracy of signs is presented in the following table:

	Percentage Accurate
Objective sensory changes.. ..	96.0
Paresis or paralysis	94.2
Facial (central and peripheral) .	91.0
Hoffman sign	90.6
Jacksonian epilepsy	90.5
Hamstring reflexes	90.0

The interesting fact concerning this table is that facial paralysis and the Hoffman sign are included. Sensory changes curiously enough are a shade more accurate than motor weakness.

Among the signs that are less accurate, the following give the percentage accurate:

	Percentage Accurate
Third cranial nerve	12.5
Sixth cranial nerve	54.3
Fifth cranial nerve (motor)	73.7
Patellar reflexes .	75.0
Fifth cranial nerve (sensory)	76.8
Subjective sensory	76.8
Achilles reflexes	77.0
Abdominal reflexes	77.5

The author comments upon the fact that, in this series, 22 patients presented a confusing clinical picture and, in those patients, the facial weakness and occurrence of Jacksonian epilepsy were the greatest aids in localization.

Mental symptoms—As an answer to the question, what is the frequency of occurrence, nature and localizing value of abnormal mental reactions during the course of a patient developing a brain tumor, Keschner, Bender and Strauss¹¹⁷ studied a series of 530 case histories in which the diagnosis of brain tumor had been verified. These observers found that there were no mental symptoms specific for cerebral tumor. The incidence

of mental symptoms is almost twice as frequent in patients with supratentorial as in those with infratentorial tumor of the brain.

Disturbance in memory is predominantly more frequent in persons with supratentorial than in those with infratentorial growths. Complex visual and auditory hallucinations are more frequent in patients with tumor of the temporal lobe. Crude auditory hallucinations are most common on the side of the tumor, whether the tumor is located above or below the tentorium. Localized tactile hallucinations indicate the parietal lobe opposite the side of the hallucination as the seat of the tumor.

Psychic disturbances of the most severe and varied types are observed in patients in whom the tumor involves both sides of the brain.

Psychogenic reactions are determined more frequently by physical or subjective disabilities and the total personality of the patient than by the location of the tumor in any one part of the brain.

The pathogenic factors in the production of mental symptoms, in the order of their importance, are (a) Involvement of both sides of the brain; (b) increased rate of development of symptoms of tumor of the brain in general, (c) rapidity of the tumor growth; (d) sudden appearance and rapid development of intracranial hypertension, and (e) supratentorial location of the tumor. The age, general condition and premorbid personality of the patient modify the quality of the mental reactions to physical symptoms.

Special Examinations—Olfactometry—In 1935 Elsberg described a new and simple method of quantitative estimation of the sense of smell. This method employed the injection of an odor into either one or both nostrils during a period of voluntary cessation of breath-

ing. Varying quantities of saturated odorized air are injected into one or both nostrils. The smallest volume of this odorized air injected during cessation of breathing that can be recognized before another breath is taken, is called the minimum identifiable odor (M. I. O.) of the substance used. Elsberg found for ease of determination and practical use coffee and citral were best substances.

Olfactory fatigue is determined by the stream injection of odors, forcing odorized air through one or both nostrils for a certain length of time and then determining the length of time it took for the patient to regain his sense of smell for the previously determined M. I. O.

These 2 procedures, the determination of the M. I. O. and degree of olfactory fatigue, have been found by Elsberg and his coworkers to be useful in the localization of brain tumors.

A critical review of the value of these determinations has been published by Elsberg and Stewart.¹¹⁸ They employed olfactometry on 300 patients, 150 which became subsequently verified brain tumor patients and 150 of which suffered from an intracranial condition other than tumor.

The olfactory tests have no value for the localization of subtentorial growths (posterior fossa) and pituitary tumors unless they have invaded the suprasellar region and compressed the olfactory pathways. This group represented 49 patients, leaving a total of 101 patients with verified brain tumors from which to base the value of the tests.

Seventy-five patients (74.2 per cent) were correctly diagnosed, 23 patients (22.9 per cent) were not localized and 3 patients (2.9 per cent) were incorrectly localized by the olfactory tests.

Tumors in the frontal region were correctly localized in 44 out of 51 patients (86 per cent). The characteristic

olfactory pattern in this region was for a small extracerebral growth, an increase in the M. I. O. (reduction of the sense of smell), and for a bilateral lesion an increase in the M. I. O. on both sides. Olfactory fatigue was not prolonged. Tumors within the frontal lobe caused an elevation of the M I O ; in other words, a reduction in sense of smell.

Tumors in the temporal region were correctly localized in 6 of the 7 patients (85.7 per cent). The olfactory pattern for these growths was a normal M. I. O , but a prolonged olfactory fatigue. The longer the fatigue period the deeper the tumor was situated. This pattern was shown in parietal and occipital lobe tumors likewise

In 81 per cent of the 150 patients who did not have a tumor, the olfactory tests gave no evidence of a localized lesion. Where a lesion was demonstrated, there was clinical evidence of such a lesion. If the olfactory tests indicated that there was a localized lesion, there was a 73 per cent probability that the patient had a neoplasm

The value of these olfactory tests is in the diagnosis of supratentorial tumors, particularly frontal and temporal lobe tumors, and the differential diagnosis of frontal and cerebellar tumors

Ayala Index --In 1923, G. Ayala suggested in the German literature the rachidian quotient as a means of ready differential diagnosis of an expanding intracranial lesion and other causes of increased intracranial pressure. The value of this index was not estimated by either English or American investigators until the paper of N. Savitsky and M. M. Kessler¹¹⁹ appeared. These writers have given us an idea of the value of the index by studying a series of 130 patients, 51 of whom had an expanding lesion within the skull and 79 had increased intracranial pressure from other causes.

The index is obtained by performing a lumbar puncture with the patient in the recumbent posture. The head and neck are kept in the same plane as that of the vertebral column and the thighs are not flexed so sharply that they cause abdominal compression. An ordinary lumbar puncture is performed and a water manometer used to take pressure readings. The patient should be completely relaxed at the time pressure readings are made and great care should be exercised in not losing any fluid before the initial pressure is taken. Savitsky and Kessler suggest that a constant amount of spinal fluid should be removed —10 cc—and then take the final pressure

The Ayala index is usually computed as the product of the final pressure and the amount removed divided by the initial pressure thus
$$\frac{\text{Final pressure} \times \text{cubic centimeters of fluid removed}}{\text{Initial pressure}} = \text{Ayala index}$$
 For example, in a case of otitic hydrocephalus,
$$\frac{250}{300} \times 10 = 8.3 \text{ (high index)}$$
 and in case of an expanding lesion
$$\frac{100}{300} \times 10 = 3.3 \text{ (low index)}$$

These authors have found that the index is of value only in cases of which the initial pressure is above 140 mm. of water

	Index Above 5.5	Index Below 5	Index from 5 to 5.5
Brain tumor	8	31	6
Brain abscess	1	11	
Intracerebral hemorrhage	—	2	—
Intracranial aneurism	—	2	—
Hypertensive vascular disease	.. 36	2	3
Hydrocephalus (otitic and sphenoiditic)	6	—	1
Menigitis	9	1	1
Subarachnoid hemorrhage	4	—	1

The greatest value of the Ayala index, according to these writers, is in differential diagnosis of otitic or sphenoiditic hydrocephalus and brain abscess. In every instance except 1, brain abscess gave an index below 5, the exception being in a patient where the abscess had ruptured into the ventricle and set up a meningitis. The second aid given by this determination is in the differential diagnosis of increased intracranial pressure caused by vascular disease and brain tumor, the presence of an index figure below 5 being in favor of a space-taking lesion. The index gives no assistance in determining the presence of a chronic subdural hematoma.

No attempt was made on the part of the authors to explain the physics concerned in the production of these figures. They stressed, however, the necessity of performing the test under uniform conditions and that special attention be directed to the details of the manometric determinations. The writer wishes to add that this test should never be performed when the patient is suspected of harboring a space-taking lesion in the posterior fossa, and in all patients whose pressure is high, unless neurosurgical means are at hand should an untoward reaction occur.

Meningiomas of the Posterior Fossa

Rasdolsky¹²⁰ reports a series of 12 cases of meningioma in which the tumor occurred in the posterior fossa. Two of the 12 tumors were on the right side, 9 on the left and 1 in the midline. Three were of the flat type, of which 2 were in the cerebellopontine angle. In none of the cases was the nature of the tumor suspected before operation.

The clinical features of these cases is the early appearance and severity of occipital headache in each patient. The length of history did not exceed a year

in 10 of the cases and in several the duration was a few months. Local tenderness on percussion is more marked in patients having meningiomas than in those of other tumors of the posterior fossa.

The average age of the patients was 38.6 years, the youngest being 28. Seven of the patients were males, 5 were females. Other observers have noticed the slight predominance of the male to the development of meningiomata. Whether this is due to a difference in structure of the meninges in men and women, or to a greater exposure of the meninges in men to trauma, is difficult to decide. One of Rasdolsky's cases suggests the probable role of trauma.

A roentgenogram of the skull does not help as much as in the diagnosis of supratentorial tumors. Roentgenographic changes in the skull were observed in only 3 of the 12 patients. In 2 instances the occipital bone at the site of the tumor was eroded and in 1 there was increased vascularization in the bone in the region of the tumor.

Rasdolsky grouped his cases into the following clinical variants:

1. Basilar type (2 cases). The tumor is frequently localized under the brain stem, making radical removal difficult. The clinical characteristics of this type are multiple paresis of cranial nerves, involvement of the long tracts and absence of the signs of increased intracranial pressure. Cerebellar signs are usually absent. The course is benign when only one side of the posterior fossa is involved, and more rapid when the tumor is bilateral, possibly owing to bilateral implication of the vagus nerve.

2. Cisternal type (2 cases). This tumor is located between the medial surfaces of the cerebellar hemisphere over the vermis. The onset of illness is usually with attacks of occipital head-

ache following moderate physical effort, otherwise the course is that of increased intracranial pressure. These patients may at any time suffer a sudden increase in intracranial pressure by descent of tumor into the foramen of magnum, causing medullary compression and death. No cerebellar signs or cranial nerve implication can be demonstrated in these patients. Usually the tumor can be removed easily. Localizing, but not pathological, diagnosis is made by ventriculography.

3 Cerebellopontine angle type (2 cases) The location of the tumor determines the clinical picture. If the tumor grows anteriorly toward the acoustic meatus, the symptoms and signs are identical with a neuroma of the eighth cranial nerve. If it grows posteriorly and laterally, cerebellar signs may predominate. The author's cases were identical with the clinical course of an acoustic neuroma. Roentgenographic changes in the region of the porous acousticus and the pyramid favor the diagnosis of acoustic neuroma.

4 Paramedian type (1 case) This variant includes tumors in the midline, between the cerebellar hemisphere or just lateral to the midline, and superior to one of the hemispheres. The chief complaint in tumors in this location are occipital pains, followed by signs of involvement of the brain stem or a quadrigeminal syndrome (paralysis of associated ocular movements). Removal of these tumors is usually very difficult because of the close association of the tumor to the venous sinuses.

5 Cerebellar type (3 cases) The location of these tumors is the lateral part of the posterior fossa, arising usually from the walls of the lateral sinus. The cerebellar hemisphere on the side of the growth is compressed, giving varying degrees of signs.

6. Supracerebellar type (2 cases). Tumors of this type lie on the superior surface of the cerebellum away from the midline. In addition to cerebellar signs, homonymous hemianopia sometimes occurs owing to compression of the homolateral occipital lobe. Cerebellar signs appear late. The cranial nerves, especially the facial, are involved only in the later part of the disease.

Pineal Body Tumors

The pineal body is subject to tumor formation. The types of tumor are various and recently S. J. Bochner and J. E. Scarff,¹²¹ in a report on a case of teratoma of the pineal body, have given embryological significance to the classification of these tumors.

The pineal gland or body arises from the epiphyseal arch or dorsal arch. As a result of its formation, all 3 embryological layers (ectoderm, mesoderm, and endoderm) contribute to the structures of the body. This fact is borne out by considering the types of tumors which have developed in association with the pineal body according to Bochner and Scarff.

Epidermoid tumors arise from cells which come from the ectoderm. This type of tumor has not been found in connection with the pineal body.

Teratoid tumors are comprised of cells originating from both ectoderm and mesoderm. They resemble dermoids, only of more limited character. It is the opinion of these authors that the 4 reported cases of dermoid of the pineal body should be classified as teratoid tumors.

Chorioepitheliomas have been reported in conjunction with the pineal body. Askanazy has reported such a case. These tumors are primarily associated with the ovary and testis and arise from fetal epiblasts. In these tumors, there is no

evidence of ectoderm or mesoderm tissue, therefore they must have a special classification.

So-called mixed tumors of the pineal body are of 2 types. One arises from the gland cells and is commonly referred to as a pinealoma. The second type arises from the supporting structure. Glioblastoma, ganglion cell tumors, sarcoma and hemangioma are representative of this type.

Although this classification includes the various types of tumors, Bochner and Scarff state that these tumors not too infrequently present evidences of cells which can have no relationship to mature cells, the possible inclusion cells or the cell groups forming it. They suggest that the pineal cells have the property of multipotentiality

The clinical manifestations of pineal tumors may be divided into 2 groups. The first is mechanical and the second glandular. The tumor by virtue of pressure upon adjacent structures causes increased intracranial pressure. This pressure may be intermittent in the nature of a ball valve. By this mechanism midfrontal headaches and drowsiness are produced. Pressure upon the quadrigeminal plate (superior and inferior colliculi) may produce paralysis of associated upward ocular movements, drooping of the eyelids and, occasionally, Argyl Robertson pupil.

The glandular picture associated with these tumors is a precocity in the somatic, genital and psychic development with actual maturity of outlook and function. The syndrome is called macrogenitosomia precox and occurs only in preadolescent males. This syndrome has been associated with 9 out of 19 embryological tumors and 4 out of a much more frequent adenomatous tumor of the pineal body. Macrogenitosomia precox usually

signifies an embryological type of pineal tumor.

Bochner and Scarff report the case of a male 7 years old who had a teratoma. This lesion gave cellular evidence of all 3 embryological layers and, in addition, presented well-formed teeth in various stages of development.

Spongioblastoma Polare

This tumor is one of the variants of the glioma and is, therefore, an infiltrating tumor. The frequency of its occurrence can be gathered when considering the statistics of Cushing. In his series of 862 cases of glioma, the spongioblastoma polare was present in 3.7 per cent (32 cases). Echols,¹²² reporting 12 cases of his own, was able to accumulate only 66 additional cases from the literature in which the diagnosis was certain. From this group of 78 cases, this author made a clinical and pathological analysis of the spongioblastoma polare.

The general position of these tumors occurred in approximately 80 per cent of all cases along the cerebral axis, from the optic nerves to the medulla. The following table gives the location of these 78 tumors

	Number of Cases	Percentages
Optic nerves and chiasm	24	31
Pons and medulla	25	32
Cerebellum	13	17
Cerebrum (various lobes)	9	11
Basal ganglia	4	5
Miscellaneous	3	4

Pathology—The physical characteristics of the tumor are reddish-gray, bluish-gray or whitish and either firm or soft. When the tumor occurs in the cerebrum or cerebellum, it may be cystic and the growth may be in the form of a mural nodule. The spongioblastoma polare very rarely presents calcium deposits.

The microscopic appearance is a cellular tumor. These cells resemble the unipolar and bipolar spongioblasts of the developing nervous system. The processes of the spongioblast are long, single and multiple. The cytoplasm of the cell is scanty and either finely granular or homogeneous. The nucleus is oval, contains scattered chromatin and usually placed in the center of the cell body. Mitotic figures and multinucleated cells are uncommon. The cells grow along nerve fibers so that the function of these may be preserved in the area in which the tumor develops for some time. Other glial cells, such as astrocytes and oligodendrocytes, may be found in the tumor and complete the pathological picture.

Diagnosis—The clinical features of this tumor are a relatively long history, averaging 23 months in Cushing's series and 17 months in Echol's, and its predilection for children and young adults, average age in these 78 cases was 17 years.

Spongioblastoma polare of the optic nerves, chiasm and tracts occurs almost exclusively in children. The tumor may invade the eye and be seen by the ophthalmoscope. Roentgen films may show erosion of the anterior clinoid process or enlargement of one or both optic foramina. By reason of the tumor's close association with the pituitary, it may cause hypopituitary dysfunction by direct pressure.

Clinically, these tumors cannot be differentiated from other gliomas when they occur in the cerebrum, basal ganglia or pons.

Treatment—Therapy is confined to *surgical removal* where the lesion is accessible and *x-ray treatment* where the lesion occurs in the pons and optic nerves and chiasm or tracts. Complete removal has been effected in certain cerebral and cerebellar tumors of this

type. When the tumor involves one optic nerve, it can be removed completely.

X-ray treatment is said to prolong the life of individuals whose tumors cannot be removed.

Prognosis is dependent upon the location of the tumor. Considering a group of 31 cases in which operation was performed, the average survival period was 26 months, with 10 patients living at the time the computation was made. The longest survival period was 11 years.

RELAPSING JUVENILE SUBDURAL HEMATOMA

Subdural hematoma is a collection of blood, either liquid or solid, occurring between the dura and the brain over one or both cerebral hemispheres. The etiology of this condition is trauma in the majority of instances but it may develop spontaneously. Although the hematoma usually manifests itself clinically from several days to several months or years after the injury, it has been known to be entirely silent and discovered at autopsy from death due to other causes.

L. M. Davidoff and C. G. Dyke^{1,2,3} bring to our attention the fact that in children a hematoma may occur as a result of a head injury. Absorption of that blood may take place spontaneously without obliteration of the sac and the child make a good recovery. Several years later a second head injury may precipitate bleeding into the already present sac and symptoms of subdural hematoma develop which require surgical intervention. To this sequence of events they have suggested the name relapsing juvenile subdural hematoma.

The basis of their observation is made upon 4 cases. The ages of these patients were 6, 14, 16 and 18 years. In each case record there was a history of a previous head injury anywhere from 5

to 11 years before admission to the hospital. The children recovered from the injury and, from 2 to 12 months prior to admission to the hospital, they sustained a second head injury from which their symptoms and signs developed, necessitating hospitalization.

In each child, examination revealed a moderate degree of increased intracranial pressure and very few localizing neurological signs. Two children presented a visible deformity of the skull, uniform enlarged head and localized protrusion of the right frontotemporal region with associated ipsilateral exophthalmos.

The findings upon which these authors base the fact that a hematoma formed after the first head injury and absorbed, leaving the sac, and the second injury to the head precipitated bleeding into the sac, are contained in x-ray pictures of the skull. In each of the 4 cases there were definite changes in the skull on the side of the hematoma. These changes consisted of (a) Elevation of the sphenoid ridge, superior orbital plate and superior orbital ridge; (b) deepening, widening and lengthening of the middle fossa; (c) disappearance of or indistinctness of the oblique line delineating the posterolateral wall of the orbit; (d) atrophy of the inferior and lateral wall of the supraorbital fissure, (e) hypertrophy of the frontal and ethmoidal sinuses, and (f) thickening of the skull.

Davidoff and Dyke explain the skull changes by the maintenance of sufficient pressure in the anterior and posterior fossa for a sufficient length of time to cause ballooning or expansion of the malleable skull of the child and atrophy of the brain. This occurs following the first head injury. Then the pressure within the skull decreases subsequent to resorption of fluid in the sac of the

hematoma. As a result of this decrease in pressure, the accessory nasal sinuses hypertrophy and the cranial vault thickens.

In those patients in which the diagnosis was made by injection of air into the ventricles directly or by lumbar puncture, there was evidence of a space-taking lesion. The ventricles were normal in size, displaced to the side opposite the hematoma, and the ventricle on the side of the hematoma was depressed slightly.

Three of the patients were treated by simple trephines and removal of the liquid clot by irrigation. The fourth patient was subjected to a craniotomy and the hematoma was for the most part liquid.

TUMORS OF THE SPINAL CORD

Diagnosis—Clinical evidences of a spinal cord tumor is always supported or refuted by special examinations. These examinations include a lumbar puncture with Queckenstedt examination, chemical analysis of the spinal fluid—quantitative protein, x-ray examination of the spine and, finally, the use of lipiodol or air to visualize the lesion.

J. D. Camp¹²⁴ has made a study of the relative merit of the x-ray examination in the localization of spinal cord tumors and has compared them with the Queckenstedt test and spinal fluid protein determinations. For this study he reviewed a series of 198 cases in which the diagnosis of spinal cord tumor was verified. In this group of cases, he found that 60 patients, or 30.3 per cent, gave roentgenographic evidence of the presence of a tumor.

Classifying the tumors according to their relationship to the spinal cord and

dura, the following interesting table was compiled:

Number of Tumors	Type	Localized by X-Ray
53	Extradural	25 (47.2%)
111	Intradural	24 (21.6%)
24	Intramedullary	3 (12.5%)
10	Filum	8 (80.0%)

198

Tumors of the filum terminate give the highest percentage of roentgen evidence, while extradural lesions caused demonstrable changes in the x-ray in 47 per cent of this series of cases.

Plotting these roentgen changes according to the pathology of the tumor, Camp found that the lipoma caused bone changes at the site of the lesion in every instance (100 per cent), the ependymoma of the filum 80 per cent, whereas the meningioma caused x-ray changes in only 9.3 per cent of the patients.

The direct signs presented in x-ray films of the spine as evidence of an underlying tumor are flattening of the pedicles, increase in the interpedicular distance as well as erosion of any of the adjacent part of the vertebra in the region of the lesion.

Erosion of the pedicles was associated with a widening of the interpedicular distance in 55 per cent of the cases, whereas 45 per cent did not show this increase in the distance between the pedicles. The normal interpedicular distance established by Elsberg and Dyke was used in this study.

Seventy-nine patients gave no evidence of bone erosion in any part of the vertebra at the site of the lesion and 74 of these showed no change in the interpedicular distance. Therefore, only 5 patients (6 per cent) showed an increase in the interpedicular distance without bone erosion. This fact shows that erosion of some part of the pedicles or body of the vertebra is the most im-

portant roentgen sign but the interpedicular distance may be increased without other bone changes in a few patients.

Comparing bone erosion with spinal fluid block (Queckenstedt) Camp found that 25 showed complete block and 9 partial block. In each instance the spinal fluid protein was increased. Ten patients in whom bone erosion was demonstrated gave evidence of spinal fluid block and 8 of these had no increase in the protein content of the spinal fluid. From these facts it appears that the x-rays are superior to the Queckenstedt examination and protein determination of the spinal fluid by 6 per cent.

The indirect method of tumor visualization, that is, the injection of lipiodol or air into the spinal canal, increases the roentgen evidence of tumor. This author did not give any statistics about this method but felt that, from his experience, lipiodol was superior to the use of air.

Dermoids of the Spinal Canal

These tumors are rare. S. W. Cross in 1934 gathered 19 cases from the literature and added 1 of his own. According to this author's survey, these tumors vary in their structure and in their relationship to the spinal cord and its membranes.

An analysis of the cases, including the 1 herem reported, reveals the following: of 20 cases, 9 were in females, 10 in males and in 1 the sex was not stated. The youngest patient was an anencephalic monster who survived only a few hours, the oldest was 64 years of age. The greatest number fell in the third and fourth decades, in which there were 11 cases. The duration of symptoms on the whole was relatively long, averaging about 10 years. One patient with a dermoid in the region of the cauda equina had had bladder disturbances for

more than 20 years. In relation to the spinal cord, 2 tumors were extradural, 10 were intradural but extramedullary, 6 were intramedullary, 1 traversed the entire central canal beginning in the medulla oblongata, and in 1 the relations were not described. As to position, 1 tumor traversed the entire central canal; in 1 case tumors were disseminated throughout the subarachnoid space, 7 were in the dorsal region, 4 in the dorsolumbar region, 3 in the lumbar region and 4 in the region of the conus and cauda equina.

C. B. Masson¹²⁵ studied the reported cases of epidermoid or dermoid tumors of the spinal cord from the standpoint of operative treatment and end result. In 11 of the 24 reported cases, operation was performed; in 6 definite improvement was reported; in 3 no statement was made as to the result; and in 2 autopsy reports were appended. In other words, if the 3 cases in which no statement is made as to result are included with the 6 having improvement, the operative result is only 37 per cent. This figure, according to Masson, is definitely lower than in the operative results of other spinal cord tumors. Two factors may play a part in this poor showing. The first of these is the nature of the lesion, extramedullary in many instances, but frequently intramedullary. The second factor is the long duration of symptoms without recognition of the cause. Long continued cord compression causes marked interference with the blood supply at the site of the lesion and permanent cord changes. Obviously, there is little if any return of function in these patients.

Masson reports a case of extramedullary dermoid which was removed at operation, at the level of the body of the eighth thoracic vertebra. The pa-

tient's motor and sensory deficit improved following removal of the tumor.

Syringomyelia

The pathogenesis of syringomyelia has been a much disputed problem since the first description of cavity formation in the spinal cord by Estienne (or Stephanus) in 1545. The term "syringomyelia" was suggested by Olivier d'Angers in 1837.

K. Tamaki and A. J. Lubin¹²⁶ review the various theories suggested for the development of syringomyelia and, by careful study of a case of their own, suggest that syringomyelia, *sui generis*, is a developmental anomaly caused by imperfect formation of the central canal by primitive medullary epithelium.

The theories which have been suggested for the disease syringomyelia are numerous. Hallopian, 1870, concludes that the primary lesion was sclerosis in the region of the central canal. Simon, 1875, described cavity formation resulting from the softening of gliomas and their subsequent absorption. He expressed the belief that the term "syringomyelia" should, therefore, be applied only to cavitation independent of the central canal. Schultze, 1888, concluded that the process was due to abnormal development of ependymal cells with subsequent breakdown of proliferated glial cells and first called the condition "gliosis." Other types of cavity formation were recognized, notably those due to trauma, inflammatory softening, degeneration of tumor tissue and primary vascular changes.

The significant pathological finding in the case of Tamaki and Lubin were bands of ependymal cells and other cell units. The authors consider the process causing these formations to be veritable "cell rests," and the basis of syringomyelia. Throughout the cord, except in

lower lumbar and sacral regions, were linear groups of ependymal cells, including many primitive spongioblasts. These groups formed a partial lining for much of the cavitation. That these cells do not grow outward from the central canal, is the fact that, in the portion of the cord where no cavities existed, there were not only long rows of these cells but scattered, circumscribed collections of similar cells forming nests. No structure resembling the central canal, either open or obliterated, could be found in these areas.

Cavitation might start, according to these observers, not at the ependymal limiting membrane but in the surrounding gliotic tissue, which underwent necrosis and subsequent absorption. This absorption was noted in all stages. The gliotic tissue which completely surrounded such areas might slough and be absorbed and the ependymal cells line the cavity. The strong ependymal limiting membrane seemed to form an effective barrier against the further advance of cavity formation.

These observers reject the view that the process is the result of tumor tissue breakdown with cavity formation. However, they admit the coexistence of tumor and syringomyelia. They support this view by the fact that the cell rests might proliferate and form the tumor.

Trauma as a cause has been ruled out by the fact that there was such a wide distribution of cell rests.

The sequence of events in syringomyelia according to Tamaki and Lubin is a developmental anomaly caused by imperfect formation of the central canal by primitive medullary epithelium. Resultant cell rests later undergo gliosis. Cavitation in the poorly nourished gliotic tissue is an end result of the process.

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PATHOLOGY, CLINICAL

By ROBERT A. KIDUFFE, A M, M D

THE "BLOOD BANK"

Among the problems attendant upon the increasing use of blood transfusion has been the securing of a promptly available source of suitable blood. In localities where large institutions are available, this problem may be solved by the organization of transfusion services and blood donor bureaus. Where the organization of such bureaus is not feasible for they must be supervised and maintained under the strictest medical supervision — attempts have been made to replace them by the use of preserved blood.

Attention was called in a preceding Service Volume¹ to studies in Russia leading to the use of cadaveric blood for transfusion, but medicolegal difficulties, and particularly public opinion, militate rather strongly against the widespread

use of this method. Nevertheless, the principle has been rather widely adopted in the increasing use of what have become known as "blood banks," by which is meant the collection and storage of blood for subsequent use in transfusions.

It should be emphasized that, while the use of preserved blood may be considered justifiable and even therapeutically advantageous in appropriate circumstances, it must be recognized that, because of its departure from the physiologic ideal, it cannot replace the transfusion of unmodified blood. Nevertheless, there are obvious and readily conceived circumstances where the immediate availability of a suitable blood may be, and has been, a lifesaving measure.

Needless to say, the organization and proper functioning of a blood bank de-

mands meticulous attention to minutia and will therefore be discussed in some detail.

Source of Blood—Blood for a blood bank may be secured from various sources. As the duration of blood storage is rather sharply defined, it is not advisable, to prevent wastage, to use the volunteer donor service as a source of blood for storage. This is better kept

While blood secured from venesection as a therapeutic measure may, when taken from suitable patients, be used for a blood bank, the most convenient source is the volunteer donor for a particular patient.

In utilizing this source it should be frankly explained before the blood is taken that, if it should prove suitable, it will be used for the patient in ques-



Fig 1—Collection of blood from donor (Am J Clin Path)

as a source for the direct transfusion of unmodified blood. For the same reason it is unwise to attempt the preservation of blood from convalescents from infectious diseases for immunotransfusions unless such blood is to be used within the limits of the storage period. Otherwise such donors are best placed on the donor's list on call.

Placental blood from healthy women has been suggested by Goodall² as a source for blood storage but while such a source may be used the amounts securable vary widely, so that this source is not entirely satisfactory.

tion, whereas, if not suitable, it will be placed in the bank from which a suitable blood will be drawn in its place. Donors must, of course, be healthy, should be selected and preferably fasting.

Collection of Blood—A number of methods for the operation of a blood bank have been described by various workers. Perhaps the simplest and most practical to date is that of Patton³ in use at the Graduate Hospital of the University of Pennsylvania, the details of which follow.

The collection unit, shown in Fig 1, consists of: (1) A graduate, 1 liter flask

of Pyrex glass; (2) a No. 8 2-hole rubber stopper fitted with 2 glass tubes, 1 straight, the other bent at right angles to serve as an air filter and vent; a 16-inch rubber suction tube fitted with a Murphy drip with cotton packing; (3) a 16-inch length of rubber tubing fitted with an adapter for the needle; (4) a 2-cc and 20-cc. syringe; (5) 1 per

attached to the adapter. *Sterile precautions and an aseptic technic are essential.*

When the vein is punctured a flow of blood is maintained by mouth suction, which has been found more satisfactory than any mechanical means, such as a rubber bulb, as these may collapse the vein if the pressure is too great. The flask is *gently* agitated during the with-

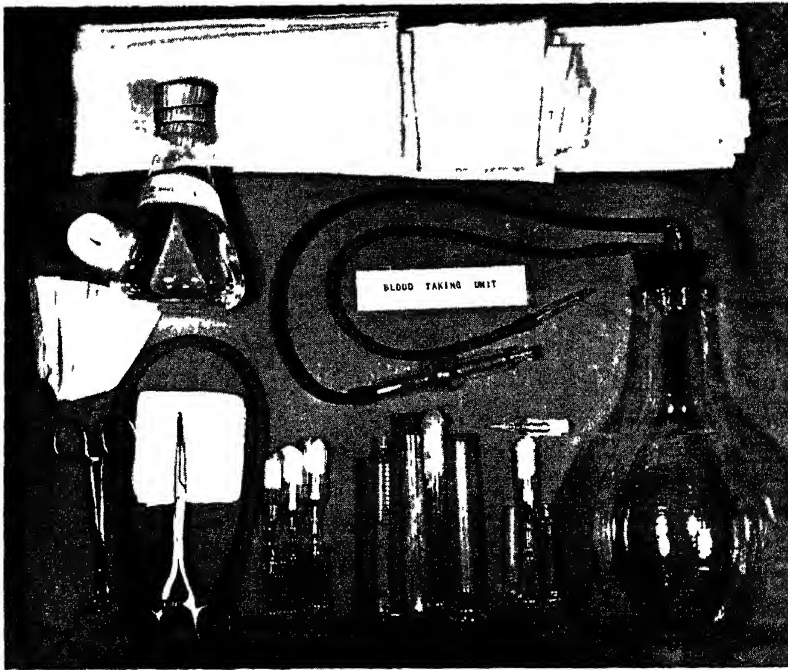


Fig 2—(Am J Clin Path)

cent novocain solution, (6) 15-, 16- and 18-gauge needles; (7) a small flask containing 70 cc. of 2.5 per cent sodium citrate solution, (8) rubber seal, paper cup and cellophane, (9) a plain sterile test tube and one containing oxalate.

The collection flask is sterilized as one part of the collection unit; the remainder of the equipment constituting the second part

The arm is prepared in the usual manner, the vein rendered prominent by a tourniquet, the 70 cc of sodium citrate placed in the collection flask, the unit assembled with the most suitable needle

drawal of blood in order to secure thorough admixture with the citrate

After 500 cc of blood has been collected, the 20-cc syringe is attached to the needle *in situ* in the vein and blood taken for the plain tube (serologic tests) and the oxalated tube (typing and compatibility tests). The collection unit is then removed from the flask, which is then sealed with the sterile rubber seal over which the paper cup and cellophane are fastened in place. An adhesive plaster label is then attached, securing the donor's name, upon which the blood type and result of serologic

tests for syphilis will be noted when these procedures are completed. A similar label is placed on the plain and oxalated tubes, which are then attached to the flask.

Storage—If for storage, blood should be *promptly* refrigerated, preferably in an electric refrigerator maintaining a constant temperature of 39° to 43° F. (4° to 6° C.). *Unnecessary handling or agitation must be avoided.*

When hemolysis is evident in the supernatant fluid the blood is unsuited for transfusion. In such case the plasma may be separated and stored for long periods for use in cases where blood protein deficit exists or in cases where cellular replacement is not a prime requisite.

Administration of Blood—Blood is administered with an administration unit shown in Fig. 2.

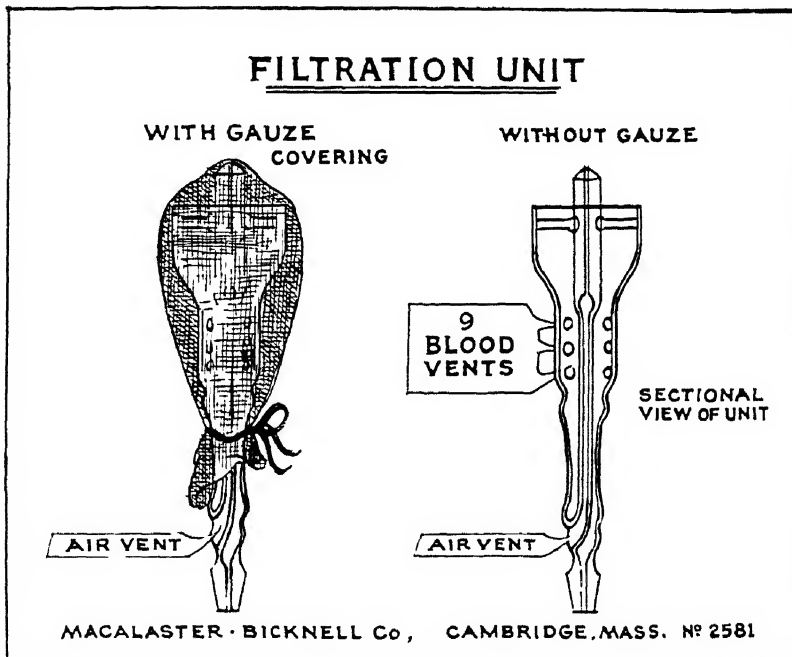


Fig 3

Obviously, only blood shown to be negative to complement fixation and precipitation tests for syphilis is stored, properly labeled as to type and with its oxalated tube of blood attached for compatibility test before use for transfusion.

Duration of Storage—In the early establishment of blood banks the period during which preservation was satisfactory varied within wide limits. It has become increasingly evident, however, that the upper limit of storage is 7 days, with 5 days as the average period after which stored blood is suitable for trans-

The administration unit consists of. (1) A specially designed filter (shown in Fig 3) covered with 3 thicknesses of 32-28 bandage gauze; (2) a 1-hole rubber stopper, (3) tubing, (4) glass adapter, and (5) 18-gauge needle.

The stopper and filter are placed in the collection flask, the edges of the stopper being folded over the lip of the flask. The rate of flow from the inverted flask is controlled by the stopcock. Air enters the flask through the air vent on the filter and prevents the production of a vacuum as the blood flows out.

The assembled administration unit is shown in Fig 4.

It is unnecessary to heat the blood before administration Careful check has also shown that cultural tests for sterility are unnecessary when the technic of collection is good.



Fig 4 -Special filter (Am J Clin Path)

Blood Bank Records A record system whereby a service may be credited with blood deposited and charged with blood withdrawn is useful and may be quite simple, as shown

Date	Service	Intern	Deposit	With- drawn
11-20	M Med	Dr Roe	500 cc	
11-23	M Med	Dr Roe	500 cc	
12-2	M Med	Dr Roe		500 cc

A master record should also be kept giving the data shown below:

Date	Donor	Col	Amt	Wass.	Precip.	Disposition
11/10/38	J Doe	Wh	500	0	0	Used, Mary Brown, W. Med 11/13/38
11/12/38	W Roe	Col.	500	44000	-2	Discarded
11/12/38	J Roe	Wh	500	0	0	Hemolyzed, discarded 11/20/38

Prevention of Reactions—The incidence of reactions in 920 transfusions using stored blood in the Graduate Hospital of the University of Pennsylvania has been 0.9 per cent. This has been attributed to the meticulous care given to the details of collection, storage and administration.

Among the important factors in this connection are: (1) Use of fasting donors; (2) avoidance of too much handling leading to agitation and cellular disintegration; (3) avoidance of heating prior to administration, (4) prompt refrigeration; (5) *meticulous cleansing of apparatus by trained personnel*

It is advisable that this be done by the Surgical Supply Room with meticulous adherence to the minutia detailed below After use the needles and syringes are flushed with water to prevent clotting and then the entire unit is given to those charged with their cleaning and sterilization in accordance with the method following

Upon Return of Set:

- 1 Disconnect all glass from rubber tubing
- 2 Treatment of rubber parts
 - (a) Place tubing on connection on water spigot and rinse with pressure for 5 minutes
 - (b) Stretch tubing rinse with distilled water and boil in distilled water for 10 minutes
 - (c) Rinse thoroughly with distilled water by attaching tubing to connection from distilled water supply 5 or 6 times
 - (d) Set up promptly and autoclave within 2 hours at least
- 3 Treatment of used glass parts
 - (a) Small parts
 - (1) Wash clean with tap water only

- (2) Boil in distilled water for 10 minutes
- (3) Rinse thoroughly with distilled water and shake dry
- (4) Connect with tubing and autoclave promptly, as before
- (b) Glass Flasks:
 - Make up soapy solution—
 - (1) Wash flasks with brush dipped in soap solution
 - (2) Rinse with cold tap water for 3 minutes
 - (3) Rinse with hot tap water for 3 minutes, with rubber tubing in bottom flask.
 - (4) Rinse thoroughly with distilled water for 6 changes
 - (5) Rack immediately
 - (6) Set up in 2 hours
- 4 Autoclave at 20 pounds for 20 minutes only.

Preparation of New Rubber Tubing—

- 1 Rinse with pressure for 2 hours.
2. Immerse in 5 per cent sodium carbonate and autoclave for 30 minutes at 20 pounds.
3. Rinse with pressure for 3 hours.
- 4 Drain

Note If not possible to thoroughly clean glassware as above, place in cleaning solution overnight and rinse with running tap water and then 5 or more rinsings of distilled water

PLUMBISM

Recent Studies for Laboratory Diagnosis—It is well recognized that lead poisoning, acute or chronic, is not solely an industrial hazard but a condition which may be encountered under a variety of circumstances being, for example, not infrequently seen in infants and young children

It is, furthermore, a condition which may at times present some diagnostic difficulty, as there is no single sign nor symptom which can be considered pathognomonic *per se*

In the absence of such pathognomonic signs or symptoms reliance is often placed upon certain laboratory findings. But, as recently discussed at some length by

Smith, Rathmell and Marcol,⁴ when dealing with toxic agents it is important that the diagnosis be made, if possible, far enough in advance to avoid or lessen the severity of a crisis

Their discussion is so comprehensive and so well correlates the present concepts of plumbism that it will be excerpted freely here

The features of both acute and chronic plumbism, which, in the aggregate, are considered of diagnostic significance in its study, have been discussed by a number of writers on this subject.

For convenience of reference, they are gathered in Table 1.

It is, of course, hardly necessary to state that not all of these signs or symptoms will be seen in any single case and it is of interest to note that it is neither always nor necessarily possible to foretell from the history and degree of exposure to lead in which group or groups (as outlined above) the presenting symptoms will fall.

As always, not the least important factor among those whose sum total is of diagnostic import is the recollection of the condition in question as a diagnostic possibility. As it is not infrequent that diagnostic possibilities for consideration emerge from the history, it is well to recall that there is a very definite individual variation in the susceptibility to lead intoxication, which explains the presence of plumbism where exposure has been slight, and also its absence where the degree and duration of exposure might justifiably awaken an expectation of its presence. While such variations in susceptibility may be inherent in the individual, they may also be influenced by the presence of various coincidental conditions, among which are anemia, malnutrition, anoxemia, vitamin deficiencies, blood dyscrasias and renal diseases

TABLE 1
(Smith, Rathmell and Marcil)
Clinical Signs and Symptoms of Plumbism

Group I Suggestive Evidence of Lead Absorption	Group II Suggestive Evidence of In- cipient Intoxication and In- active or Arrested Plumbism	Group III Suggestive Evidence of Defi- nite, Advanced, and Active Plumbism with Acute Manifestations
General Symptoms		
Patient becomes easily flustered, moody, restless and excitable General feeling of malaise	Pallor Jaundice Slight lead line Arthralgia Slight inanition Fatigued easily Hypotension to normal Slight pyrexia	Anemia Inanition Lead line Arthralgia Jaundice General weakness Hypertension Pain in chest Wrist drop Foot drop
Digestive System		
Persistent metallic taste Slight anorexia Slight constipation	Metallic taste Coated tongue Anorexia Constipation Slight abdominal colic	Metallic taste Coated tongue Anorexia Marked constipation Paroxysmal colic Nausea and Emesis Rigid abdomen Blood in stool
Nervous System		
Irritability Unco-operativeness	Slight frontal headache Slight tremors to Parkin- sonian syndrome Slight ataxia Insomnia Palpitation Increased reflexes Increased irritability Eye grounds may show choking of optic discs	Severe frontal headache Tremors Confusion Ataxia Insomnia Convulsions Fibrillary twitchings Neuritis Visual disturbances Encephalitis Hallucinations Coma Paralysis Cerebral palsy
Renal Symptoms		
Lead which fluctuates between normal limits and a very slight rise.	Trace of albumin and few granular casts in urine Lead which fluctuates be- tween normal limits and a positive rise	Toxic nephrosis Albuminuria Casts in urine Hematoporphyrinuria Hematuria Positive but fluctuating lead findings

When the possibility of plumbism has been overlooked, however, it may be and has been confused with cord and intracranial tumors and even with appendicitis and gall-bladder disease, thus leading to unnecessary surgical intervention.

Among the more familiar evidences of lead poisoning perhaps the "lead line" on the gums, the white lines demonstrable by radiography in growing bones in children, and the stippling of the erythrocytes are apt to be recalled first.

That there are of definite value and have a definite place in the study of plumbism is rather generally recognized. But, as Smith, Rathmel and Marcil point out, it is well to remember that, when found, such manifestations require careful interpretation.

The "lead line" on the gums, for example, may be due, not to lead but to bismuth intoxication. While the fact that lead storage takes place largely in bone is the basis for the radiographic evidence of plumbism in children, it is of importance to emphasize the necessity for careful interpretation of the white line demonstrable by x-ray.

First of all, in the adult the storage of lead in bone is more marked in the trabeculae than in the cortex; while in children the highest concentrations occur in the areas where calcification is most actively in progress. The demonstration of white lines at the costochondral junctions is hence of definite diagnostic significance except after the age of 10 years, when it is of no significance and cannot be used as an evidence of plumbism.

It should be emphasized also that prognostic inferences cannot be based safely upon the width of the white line shown in the radiograph because, first, the width of the line depends largely upon the amount of growth which has occurred during the period of lead ingestion, and, second, because there is no necessary re-

lation between the width of the line and the amount of lead ingested. For even when the ingestion of lead has been of sufficient degree to cause death from plumbism, the white line may be quite narrow if *the lead ingestion has occurred over a short period of time*; whereas a much smaller amount sufficing to produce only mild symptoms may produce a large line if the period of ingestion was long.

And, finally, the white line is not *per se* pathognomonic of plumbism as it may be seen, not only in the case of bismuth, strontium and phosphorous intoxication, but also in cases where bone growth has ceased, as in adults and cretins.⁴

It is, of course, natural to look upon the detection of lead in the body fluids or excretions as constituting definite evidence of lead intoxication. Unfortunately, however, there is not available at present a satisfactory clinical method for the determination of lead in the urine. Moreover, even when, through extensive chemical investigation, lead is demonstrated in the urine, the findings are of little diagnostic value from the standpoint of diagnosis.

For, as has been amply demonstrated by investigators in all parts of the world, lead is excreted in varying quantities in the urine of normal individuals. The degree to which the normal excretion of lead occurs varies somewhat, influenced, perhaps, somewhat by the variations in the method of examination used by different workers, somewhat by the chemical and physical characteristics of the lead salts and preparations to which the individual may have been exposed; and not a little by the various factors which may influence the character and amount of urinary excretion. Among these latter may be mentioned edema, dehydration, imbibition and, of course, diseases of the kidneys.

From the combined statistics of numerous workers, the normal excretion of lead in the urine of normal individuals may be given as from 0.02 to 0.08 mg. per liter or from 0.05 to 0.010 mg. per 24 hours.

In the urine of patients suffering from plumbism, the excretion of lead has varied from 0.033 to 0.394 mg., to 0.15 to 0.64 mg. and has even reached as high as 62 mg. per liter.

Obviously, therefore, the significance to be attributed to the demonstration of lead in the urine depends, not upon its presence, but upon its determination in amounts in excess of those which may be found in normal urine.

It has been shown that the excretion of lead in the urine immediately after the cessation of severe exposure is rarely in excess of 0.30 mg. per liter and drops so rapidly that, by the time the 24-hour specimen has been collected, it may be as low as 0.15 mg.

Nor does it follow that exposure to lead will necessarily lead to urinary excretion of lead beyond the normal limits. In 356 workers exposed to lead hazards in connection with ethyl gasoline the urinary excretion of lead was within the normal range (0.02 to 0.08 mg. per liter) in 63 per cent.

From these, as well as similar studies available but not here quoted, it is apparent that lead determinations in the urine are of relatively little value in the clinical study of plumbism and can only be considered of significance when the excretion is 0.20 mg. per liter or over.

Of still less value as a diagnostic indication is the determination of lead in the feces, as shown by many investigators whom it is unnecessary to quote in detail.

The demonstration of varying degrees of anemia consequent upon the absorption of lead into the blood stream is one of the signs in conformity with the diag-

nosis of lead intoxication which the clinical laboratory may be called upon to demonstrate. The anemia of plumbism has been shown to be due mainly to an abnormal destruction of the circulating erythrocytes rather than to a decreased production, which latter does not form a part of the picture of lead intoxication until the condition has reached its last stages. A *sudden* drop in the hemoglobin and erythrocyte count is, therefore, of ominous import as reflecting bone marrow degeneration.

The effect of lead upon the erythrocytes has been shown by experimental investigations to comprise the following:

1. An alteration in the surface of the erythrocyte leading to (a) shrinkage, (b) inability to swell as does the normal corpuscle, and (c) an increased fragility, leading to hemolysis on slight trauma.

2. A loss of the normal viscosity.

3. A loss of agglutinability by the different isoagglutinating serums.

This failure to react with blood grouping or typing serum is, without doubt, the explanation of some, at least, of the transfusion reactions recorded in cases of plumbism.

As these changes, which are mainly on the cell surface, lead to a reduction in the number of erythrocytes in the peripheral blood, a compensatory regeneration is inevitable so that many young and often immature erythrocytes are forced into the circulation. But as they are at once subjected to contact with lead leading to coagulation of their basophilic substance, the resulting reaction to polychromatic blood stains produces an appearance familiarly known as "stippling," and perhaps of all the procedures which the clinical laboratory may be called upon to use in the clinical study of lead intoxication, the request to look for stippled cells is certainly not the least common.

As the frequency of this request suggests an intimate clinical association of stippling with plumbism, the phenomenon may well be discussed with profit.

In the first place, while both stippling and what is commonly spoken of as basophilic degeneration are both indicative of changes in the basophilic substance of young red cells, they are now regarded by the majority of hematologists as differing in principle, rather than merely in degree, and also as of differing significance.

The term *basophilic degeneration* is now rather generally restricted to the appearance of the basophilic substance in relatively large clumps within the cell and is regarded as an evidence, not of degeneration of the cell, but of *regeneration*, as was formerly thought. So that, to that extent, the term is now a misnomer.

Stippling, on the other hand, is now used to denote the presence of basophilic substance in fine, punctate dots providing a feathery stippled appearance which is seen whenever the products of red cell destruction are retained in the body.

However, it should be mentioned that some observers regard polychromasia (polychromatophilia), punctate stippling and reticulation as but different manifestations of the presence of basophilic substance, while others have shown that the appearance of basophilic substance as polychromasia, punctate basophilia (stippling) or reticulation depends in some degree, if not largely, upon the particular staining method employed.

The present writer is not disposed either to dispute or contend against these observations and, indeed, is in large measure in accord with them. He is in agreement with the rather numerous group who hold that stippling, polychromasia and reticulation are all substantially the same substance and all due

to the presence of basophilic cytoplasm of youthful origin.

In the evaluation of erythrocyte stippling as a diagnostic criterion in the clinical study of lead intoxication, it should be strongly emphasized, first of all, that stippling, while it occurs in lead poisoning, is *not pathognomonic of plumbism*.

Stippled erythrocytes may be seen, not only in small numbers in normal blood, and in somewhat increased numbers in the presence of anemia, but may be quite frequently encountered in more or less marked degree in a variety of conditions. Among the diseases associated with a marked increase in stippled cells are intoxications with copper, benzene, arsenic and aniline products; following gold injections; poisoning by xylene, toluol and chlorinated hydrocarbons, anemias, both secondary and primary (pernicious); polycythemia; leukemia, hemolytic jaundice, cachexia following malaria or associated with malignant neoplasms, malignant toxemia, and even following a change to a high altitude.

It is obvious, therefore, that though stippling is a rather frequent concomitant of plumbism, and especially in the acute stages, it is certainly not to be regarded as a pathognomonic manifestation of this disease.

On the other hand, when properly evaluated, stippling is of definite significance and this examination has a definite place in the clinical study of lead intoxication as contributing something to the sum total of the requisite diagnostic criteria.

In an attempt to confer definite and clear-cut significance to the study of blood smears in plumbism, McCord and associates proposed the "basophilic aggregation test" based upon the enumeration of the total number of basophilic containing cells (basophilic aggregation) in distinction to the stippled cells.

TABLE 2

Relation of Basophilic Stippling, Reticulocytic Count, and Basophilic Aggregation to the Development of Clinical Symptoms in Acute, Chronic, and Induced Plumbism

	Stippling				Reticu- locytes			Basophilic Aggregates			
	None	Few-0 2%	0 2-0 9%	Over 1%	None-1 5%	1 6-4 0%	Over 4%	None-1%	1 0-1 5%	1 5-2 0%	Over 2%
Total Number of Cases Examined		101				45			58		
During Symptoms of Group I	14	7	0	1	0	0	0	2	1	0	4
Preceding Onset of Symptoms of Group II and III.											
Over 28 Days	0	0	0	0	0	0	0	0	0	0	0
28 to 14 Days	0	1	0	0	0	0	0	2	0	0	0
14 to 7 Days	0	1	0	0	0	0	0	0	1	0	0
7 to 0 Days	0	3	0	0	3	0	0	0	1	1	1
Total	0	5	0	0	3	0	0	2	2	1	1
During Toxicosis Symptoms of Group II and III	27	11	3	1	17	8	2	9	2	6	5
Following Subsidence of Symptoms											
0 to 7 Days		4	1	2	3	0	2	4	1	0	4
7 to 14 Days		3	3	3	2	2	0	1	2	0	0
14 to 28 Days		5	1	1	2	1	0	2	0	1	2
Over 28 Days	3	2	1	3	3	0	0	4	0	1	1
Total.	3	14	6	9	10	3	2	11	3	2	7

(Courtesy, Am. J. Clin. Path., Sept., 1938)

According to their studies, the number of basophilic erythrocytes in the normal adult rarely exceeds 1 per cent while workers exposed to lead but without clinical manifestations showed from 1.5 to 4 per cent, the number rising as high as 20 per cent. Values of 1 to 1.5 per cent therefore represent a threshold zone of doubtful interpretation, values of 1.5 to 2.0 per cent in workers exposed to lead suggest lead absorption and the possibility of approach to clinical lead intoxication; and values over 2 per cent are diagnostic of plumbism.

However, the basophilic aggregation test has not been found reliable by other workers who have studied it as increases comparable to and even exceeding those suggested as diagnostic of plumbism have been found in other conditions associated with the production of stippling.

Attempts to base significant inferences upon quantitative estimations of reticulocytes, punctophilia, polychromatophilia, basophilic aggregation and the presence of normoblasts, while in the aggregate of some little suggestive value in assisting to establish plumbism as a diagnostic possibility, have failed to confer any prognostic significance to these procedures.

This is shown in Table 2, taken from Smith, Rathmell and Marcil.⁴

Various observers have studied the effect of lead intoxication upon the leukocytes and have demonstrated a rise in the lymphocytes and monocytes and a shift to the left in the early stages of plumbism. The total leukocyte count is inconstant, some cases showing a leukocytosis, others a leukopenia.

Smith, Rathmell and Marcil comment that the change in the leukocyte picture

precedes the development of recognizable clinical evidence of plumbism and therefore regard it as of some contributory value.

They believe, however, that the laboratory study of lead intoxication should comprise an accurate determination of lead in the serum, cells and fibrin fraction of the blood, methods for which are given in detail in their article.

These determinations, when considered in relation to the total amount of lead in the whole blood, these workers believe not only of diagnostic but of differential diagnostic value as enabling a distinction, not only between acute, chronic and mild lead poisoning, but also as enabling a distinction between mild lead intoxication and such conditions as hypercalcemia, gastroenteritis, food poisoning, sun and x-ray burns, and colic from various causes.

They also advocate the use of these procedures whenever lead is used as a therapeutic measure (as in the treatment of malignancy) as a measure of control of value in foreseeing and preventing the development of an acute lead crisis.

These observers give the normal lead content of blood as follows:

Mg. Lead per 100 Gm.	Serum	Cells and Fibrin Fraction	Whole Blood
Maximum	0.000	0.002	0.001
Minimum	0.000	0.011	0.006

No essential difference in the lead content of the blood in health and disease was found. The values given above were independent of sex, age, climatic changes, daily fatigue, violent exercise, meals, menstruation and ovulation.

In plumbism the appearance of lead in the serum fraction of the blood, an increase in the lead content of whole blood and a Type 4 shift of the neutrophils and hemogram (Crocker) is evi-

dent in proportion to the degree of plumbism.

There appeared to be a direct relationship between fatalities and lead blood crisis, as well as a direct relationship between lead blood crisis and clinical symptoms.

During the former there is a tendency for the lead in all fractions to assume the same value, the absolute amount depending upon the severity of the plumbism, while in the latter there is an increase of lead in the serum fraction usually accompanied by an increase in the whole blood lead content.

In the last analysis the important factor is the appearance and disappearance of lead, in amounts beyond the normal range, in the serum fraction of the blood.

PHOSPHATASE DETERMINATIONS

Clinical Applications — Following the custom that enzymes or biochemical catalysts derive their names from the substances upon which they act, *phosphatase* denominates the enzyme which splits the phosphoric acid esters of carbohydrates. Phosphatase therefore acts upon phosphoric esters as lactase acts upon lactose or maltase upon maltose.

That certain tissues possess the specific property of hydrolyzing phosphate esters in the body was first suggested as long ago as 1923 by Robison and again in 1925 by Northland, who demonstrated the liberation by phosphates of free phosphoric acid from glycerophosphates, hexosephosphates and nucleotides, and further demonstrated a very active phosphatase in preparatory areas of ossification.

From these findings it was postulated that phosphatase, through hydrolysis of

the phosphoric esters, increased the concentration of PO_4 ions and that, as a result, the solubility product of calcium phosphate was exceeded and that this was then deposited in the ossifying zone.

These early observations were soon corroborated by many investigators with the result that, under appropriate conditions, phosphatase determinations are becoming of definite clinical value and significance.

It has now been quite definitely established that, while phosphatase is fairly ubiquitous in the body, it occurs most abundantly in the red blood corpuscles, plasma, renal tissues, muscle extracts and in actively growing bone and cartilage. It is *not* found in such nonossifying cartilages as the trachea, Meckel's cartilage or rib cartilage.

It has been shown the source of phosphatase is the osteoblast, and from this observation in conjunction with the fact that phosphatase is found wherever ossification is taking place, is most abundant when the deposition of calcium salts is most active and hence is more abundant in actively growing than in adult bone, the importance of phosphatase determinations in disease processes arising in or related to pathological processes affecting the osseous system becomes apparent.

The chemical factors influencing ossification may be regarded as (*a*) a sufficient concentration in the blood of inorganic phosphate and physiologically active calcium, and (*b*) a proper functioning of the factors leading to the localized deposit of calcium phosphate and carbonate.

The relation of disturbances in the concentration of phosphorus and calcium in the plasma to disease processes related to the osseous system has long been recognized, as in rickets, for example. But it has been somewhat puzzling at times to find both determinations within normal

limits in the presence of undoubted rickets, just as it has been disconcerting to the assumption that nonunion in fractures is the aftermath of calcium deficit when the blood calcium determination reports a normal concentration.

Such findings, however, become somewhat more understandable in the light of available studies of phosphatase. For, though the formation of the skeletal calcium phosphate is influenced by the concentration of phosphorus and calcium ions in the blood, it is now apparent that the phosphate ions are supplied by the hydrolysis of phosphate esters by the enzyme phosphatase. Hence, though the circulating plasma may be assumed to be supersaturated with calcium phosphate, it cannot be precipitated until by the addition of Ca or PO_4 ions, the other ion is driven out. When excess PO_4 ions are liberated by the hydrolyzing effect of phosphatase, more calcium phosphate is formed and deposited as an excess in the bones. And, as phosphorus ions occur in a multitude of forms, whereas calcium ions exist almost exclusively as carbonate and phosphate, the retention and excretion of the body calcium may be considered as almost entirely dependent upon the concentration and supply of inorganic phosphate.

Investigative studies have definitely shown that the *relative* amounts of calcium and phosphorus in the blood are more than the absolute amounts and as later studies have indicated, phosphatase is of definite significance in this connection.

The normal distribution of phosphatase has already been touched upon. It may be added that the phosphatase content of bone decreases with age and in the adult is comparatively small. That it persists at all in adult bone, Kay suggests, may be a protective mechanism assuring throughout life a slight excess

of PO_4 ions in the vicinity of already deposited bone.

Phosphatase activity is expressed as phosphatase units representing the amount of enzyme liberating 1 mg. of phosphorus under controlled factors of time and temperature.

Unfortunately, in the early stages of these investigations there was definite variation in the time of incubation and the incubation temperature used by various workers resulting in some confusion as to the value of the phosphatase unit. Thus, the lowest normal value for the adult ranges from 0.10 to 0.21 units (Kay), and the highest normal value for the adult from 33 to 49 units (Lundsteen and Vermehren). In children the lowest normal value ranges from 0.17 to 0.34 Kay units and the highest normal value from 156 to 241 units (Lundsteen and Vermehren).

While these differences render actual comparisons somewhat difficult, the trend of phosphatase determinations (decreased or increased) is nevertheless quite clear and makes clinical deductions possible.

At the present time phosphatase determinations are generally reported in terms of the unit proposed by Bodansky and normal ranges are accepted as, for adults, 1.5 to 4 Bodansky units per 100 cc. of serum, and, for children, 3.1 to 13.1 units per 100 cc. of serum.

Phosphatase determinations are not technically difficult and consist of the estimation (a) of serum phosphate, and (b) serum phosphate plus the phosphate liberated by the phosphatase from a known volume of glycerophosphate added to the serum.

Phosphatase units are determined by the formula $b - a = \text{phosphatase units}$

Phosphatase determinations have now been reported by numerous investigators in a variety of conditions many of them, quite naturally, related to disease proc-

esses affecting the bony structure, and it is now possible to summarize the clinical applications and significance of phosphatase determinations more or less as shown in the following paragraphs.

Among the problems with which the surgeon may be confronted is that concerned with the *nonunion of fractures*. While this complication has usually been attributed to a calcium deficit, this assumption has not infrequently been overthrown by a blood calcium determination within normal limits and it must be admitted that, even when hypocalcemia is demonstrated, nonunion may represent the product of several factors, just as diabetes is a multiple disorder of which glycosuria is only one manifestation.

The application of phosphatase determinations to the study of experimental fractures in animals has been studied with results as yet purely of academic interest. They demonstrated that the phosphatase content was much higher in the region of healing fractures than in uninjured bone and correlated this with the parallel osteoblastic activity seen in sections. The natural suggestion that phosphatase powder be used in cases of nonunion has not, however, been followed by much success.

Studies of phosphatase activity in non-malignant, low-grade malignant, and malignant bone diseases have been reported by various investigators with findings which may be thus summarized:

1 In *nonmalignant bone tumors* phosphatase is normal or low

2 In *Ewing's sarcoma* and *multiple myeloma* phosphatase is normal or slightly elevated

3 In *malignant disease metastatic in bone* there is a considerable increase in phosphatase, which finding thus becomes of importance in differentiating the bone metastases of carcinoma from multiple myeloma and endothelial myeloma.

4. Phosphatase is greatly increased in *osteogenetic sarcoma of the osteoblastic type* but not in the nonossifying type. After surgical treatment of such lesions the phosphatase content of the plasma falls in from 14 to 21 days. An increase is associated with demonstrable metastases.

In view of the difficulty which may be experienced in the differentiation by means of x-rays between multiple myeloma without Bence-Jones protein and multiple bone metastases in carcinoma, phosphatase determinations are of definite value, an increase indicating malignancy.

It must be remembered, however, that as jaundice produces an elevation of the blood phosphatase level, no conclusions as to the nature of bone tumors can be drawn from phosphatase determinations in the presence of coincident icterus.

The intensive studies of phosphatase levels in the presence of bone lesions have so far shown it to be increased in the following conditions. In conditions associated with active bone formation and in those which have been described as representing "frustrated attempts at osteogenesis"; in rickets, hyperparathyroidism (generalized osteitis fibrosa cystica, Von Recklinghausen's disease of bone), osteitis deformans (Paget's disease of bone) and in the osteoblastic type of osteogenetic sarcoma.

Among the more recent studies of phosphatase in connection with lesions of the bones is that of Roe and Whitmore,⁵ who report cases illustrative of the clinical utility of phosphatase determinations. One case reported by these authors was an aleukemic leukemia of the lymphoid type with extensive bone involvement in which a phosphatase determination within the lower normal range for the age (9 years) enabled a differentiation from hyperparathyroidism.

The increased phosphatase determinations encountered in diseases of the liver, and especially those associated with jaundice, have been thoroughly reviewed by Cantarow.⁶

It has been established by various workers that phosphatase is invariably high in *gross obstructive jaundice*, such as that produced by common duct obstruction by stone or pancreatic malignancy, whereas in other forms of jaundice the phosphatase level is normal or only slightly elevated. Phosphatase determinations are thus of greater differential significance than the Van den Bergh or icterus index, though these latter are of great use in following the degree and course of jaundice.

The reason for this sharply demarcated difference in the phosphatase level in obstructive *versus* nonobstructive jaundice is not quite clear as yet.

The assumption that it arises from the presence of inhibitory substances in the blood in toxic jaundices has not been substantiated by the demonstration of such inhibition.

A further assumption considers that bile is rich in phosphatase and that when bile is dammed back by obstruction phosphatase automatically increases.

However, experimental studies have failed to demonstrate sufficient phosphatase activity in bile to account for the high phosphatase levels encountered in obstructive jaundice.

A somewhat significant observation is reported in this connection, namely, that whereas bile pigments are readily excreted in the urine, phosphatase is not. The mechanism responsible for the increased phosphatase levels in obstructive jaundice still remains to be found.

A study of phosphatase activity as well as of changes in the serum calcium and inorganic phosphate in *pregnancy* is re-

ported by Bodansky,⁷ the results of which may thus be summarized:

Up to the seventh lunar month, 83 per cent of the results fell within the normal range for adults (1.5 to 4 Bodansky units), 15 per cent being between 5 and 6 units.

During the seventh month, a definite change in the pattern took place, which progressed throughout the remainder of pregnancy, this change being an increase in the amount of phosphatase.

The reversal of distribution is shown by the average mean values as follows: Second to sixth lunar months, 2.93 units; seventh month, 3.23 units; eighth month, 3.57 units; ninth month, 4.7 units; tenth month, 5.9 units; and at labor, 6.6 units.

A similar increase in the phosphatase activity during pregnancy is reported by Meranze, Meranze and Rothman.⁸

These authors suggest, as an explanation for the increase, either that the phosphatase elevation may represent a pathologic or potentially pathologic state of bone metabolism in mother or fetus, or, perhaps, more probably, that as the rise is coincident with the greatest activity of fetal ossification it coincides with the period of greatest phosphatase need. In support of this contention they point out that as the fetus does not elaborate much phosphatase the rise in the maternal phosphatase may represent a compensatory increase.

Bodansky is inclined to relate the progressive increase in the maternal phosphatase level to the increased lability of the maternal bone metabolism, recalling the view advanced by Bodansky and Jaffé that the serum phosphatase is an expression of the "controlled specific reactivity" to resorption of bone (normal and pathologic).

The development of varying degrees of demineralization in pregnancy, especially under conditions of inadequate mineral

intake, and, indeed, even when the intake of calcium and phosphorus is adequate, is most probable, as M. Bodansky shows.

Experimental studies have shown that the removal of calcium from bone is in all probability controlled by the parathyroids. During pregnancy the tendency to hypocalcemia increases because of the demands for fetal growth but is ordinarily compensated for by an increased parathyroid activity so that pregnancy may therefore be regarded as normally associated with some degree of hyperparathyroidism and that, therefore, an increase in the plasma phosphatase level may be expected on these grounds.

From these various studies it would appear that phosphatase determinations may be expected to become of increasing clinical interest as the results of further investigations accumulate.

PNEUMOCOCCUS TYPING

Present Status—The widespread inauguration of pneumonia control campaigns has focussed attention upon the necessity for early administration of anti-pneumococcus serum and, as a corollary, upon the urgent necessity for rapid type determination of the pneumococcus strain responsible for the disease.

As a consequence, the method now attracting the greatest attention is that first described many years ago by Neufeld and now revived as the "*quellung*" (capsule-swelling) reaction.

The *quellung* reaction depends upon the fact that when the pneumococcus is brought in contact with homologous antipneumococcic agglutinating serum a distinct and often marked swelling of the capsule occurs, thus establishing the type of pneumococcus.

The procedure in principle is relatively simple and may be briefly described as follows:

1. The presence of pneumococci in the sputum to be examined is first established by examination of a gram-stained smear. It is not necessary that the organisms be numerous; typing can be established with very few organisms and, indeed, can even be demonstrated with a single pneumococcus.

2. A small portion of sputum (removed with a sterile platinum loop, or snipped from very tenacious specimens with flamed manicure scissors) is placed on each of several cover glasses or on each of several marked areas of a glass slide.

3 To each bit of sputum add 2 to 3 times the volume of typing serum, and mix. The preparations are now covered with a cover glass and examined under the microscope.

4 Preparations are examined at once and if no reaction is seen a final reading is made after 30 minutes.

A positive reaction is shown by a decided swelling of the capsule, which shows a very definite outline. In a negative reaction there is no swelling and the capsule appears as a halo without a definite outline.

As the procedure has been widely advocated as one of great simplicity and thus suitable as an office method, it is not without importance to call attention to the details essential to its successful use.

In the first place, the *quellung* reaction cannot be elicited consistently with the ordinary pneumococcus agglutinating serums prepared from the horse and heretofore used for macroscopic agglutination tests. Typing serum for the Neufeld reaction must be prepared from rabbits for this specific purpose.

Such serum is commercially available and is securable, not only for each specific type, but also in group combinations. The latter, comprising several

groups, are used first and, if a negative reaction occurs, several types are eliminated by a single examination. When a positive reaction occurs with group serum, the test is then repeated with each of the serums in the group.

In order to render the reaction more visible, Neufeld typing serums are supplied with the addition of a small amount of methylene blue stain. This supplies a background in which the capsule swelling is more easily seen and at the same time stains the diplococci.

Not the least important essential prerequisite is a familiarity on the part of the observer with the morphology of the pneumococcus and the appearance of the positive and negative reaction. A good microscope and ample illumination are necessary and an artificial blue light, secured by the insertion of a disc of a blue glass in the substage, is advantageous.

Despite its apparent simplicity, the widespread use of the Neufeld reaction has brought to light many factors which influence its occurrence and interpretation, the more important of which are noted in the paragraphs to follow.

It is, of course, obvious that the specimen examined must consist of true sputum and not secretions from the mouth or nasopharyngeal mucus "hawked up." For, as is well known, pneumococci are more or less common inhabitants of the upper respiratory tract and hence may be present and satisfactorily typed in such material. Such typing, however, will not necessarily indicate the type of pneumococcus present in the lung and responsible for the pneumonia and will hence lead to the use of an ineffective type of therapeutic serum.

Even when the specimen has been carefully procured and the procedure properly carried out, the Neufeld reaction will fail in approximately 10 per

cent of cases, and in a smaller proportion anomalous type reactions may occur.

For these reasons the typing by the Neufeld reaction should preferably be checked and controlled by typing of cultures or by mouse inoculation, and either or both of these methods are necessary when no reaction is obtained in the sputum directly by the Neufeld procedure.

In order to avoid destruction by autolysis of the pneumococci in the sputum, the test should be carried out on specimens not more than 2 hours old although, if the sputum is kept on ice, satisfactory reactions are obtained after several days.

Harris and Varley⁹ report that the *quellung* reaction can be obtained from sputum preserved with 1 per cent formalin (40 per cent formaldehyde). Preservation is satisfactory for Types I, II, VIII and XIV but *not* with Type III. Sputum containing pneumococci of the groups indicated can thus be preserved for demonstration and teaching purposes.

It is apparent, of course, that specimens thus preserved by the addition of formalin cannot be used for culture or mouse inoculation, should these be necessary or advisable.

Brown¹⁰ has recently shown that autolysis and capsular damage by the contaminating overgrowth of other bacteria can be eliminated by smearing the sputum on a glass slide and allowing the smear to dry. Such dried smears can be stored for future examination or safely transported for immediate examination on receipt. The typing serum is simply placed on the dried smear and the examination made as usual.

A reversal of this procedure is also possible. The type serum is allowed to dry on the slide and the sputum added to it. The reaction occurs as usual.

Among the complications which may not only delay the process of typing but

also impair its accuracy are: (1) The fact that pneumococci may be so scarce in the sputum as to make it difficult and tedious to make sure that no *quellung* reaction has occurred; (2) the presence of cells and detritus in the specimen may render the recognition of pneumococci difficult and delay the appearance of the reaction, and (3) the variation in 1 and 2 which occurs in different portions of the same sputum may be a cause of delay and difficulty.

To eliminate these difficulties Taplin, Meneely and Hettig¹¹ describe a *quellung* concentration method, the technic of which follows:

- 1 The entire specimen of sputum is emulsified and large particles broken up by drawing it up into a small (2 cc) syringe and mixing it thoroughly in a Petri dish

2. In a sterile centrifuge tube place 0.5 cc of the emulsified sputum and, depending upon its viscosity, add 6 to 10 cc. of normal saline solution. Emulsify by drawing back and forth in a sterile 10 cc pipette.

3. Centrifuge at 1000 r p m. for 2 to 3 minutes to remove cells and detritus, the bacteria remaining in the supernatant fluid

- 4 Transfer the supernatant fluid to another tube and centrifuge 10 minutes at 3000 r p m. Then pour off all but about 0.25 cc of supernatant fluid above the sediment

- 5 Resuspend the sediment by shaking and use the suspension for typing tests

These authors prefer to add 2 drops of methylene blue to the suspension before making preparations for the addition of typing serum because, in many cases, when stain and typing serum are added simultaneously, swelling may occur before staining and obscure the recognition of the organisms.

It may be noted in passing that pneumococcic typing is applicable, not only to sputum, but also spinal fluid, pus, cultures, etc., in fact, to any material containing pneumococci.

Schaub and Reid¹² have described a microscopic precipitin test applicable to

pneumococcus typing, the technic of which is described below.

Preparation of the Antigen—Cultures of pneumococci from blood, spinal fluid or other sources taken during life or at autopsy may be grown in meat infusion broth containing a few drops of serum or ascitic fluid incubated at 98.6° F. (37° C.) for from 6 to 18 hours. The culture is lysed by the addition of 2 drops of a 10 per cent aqueous solution of sodium desoxycholate (containing 1:50,000 merthiolate to prevent the growth of moulds) per cc. of culture. In from 15 to 30 minutes the organisms are dissolved, and tests have shown that the lysate is sterile. The antigen is now ready for use. In some instances an excess of sodium desoxycholate in the presence of serum will cause the culture medium to gel. This may be liquefied by warming slightly without decreasing the efficiency of the test.

Preparation of the Typing Serum—For making this test, horse antipneumococcus serum such as is used for macroscopic agglutination tests, diluted 1:10 in physiologic solution of sodium chloride, is used. Such dilutions have been found satisfactory after refrigeration for as long as 6 weeks.

Technic of the Test—The Petri dish hanging drop technic described by Brown is used for making the test. A disc of moist filter paper is placed in the lid of the dish. The bottom of the dish is ruled on the bottom surface with a wax or diamond pencil, providing 16 12 mm squares. In the performance of the test 2 Petri dishes are required for each organism to be typed. In one dish the antigen is set up against each of the 15 types of antiserum (diluted), the sixteenth square being used for an antigen-salt control. In the second dish the remaining type antisera are set up. It has been found most practicable to

add 1 platinum loopful of the antigen to each of 5 squares and mix them with an equal amount of the appropriate typing serums, and then to proceed with the next 5 squares in the same manner. This prevents drying of the loop of antigen before it is possible to add the antiserum, as is likely to happen if the antigen is placed in all 15 squares before the antisera are added. A 2 mm. loop of platinum rather than one of the platinum substitutes is recommended. The loop should be thoroughly flamed and cooled each time before being introduced into the serum.

Reading of Results—The mixtures of serum and antigen are held from 15 to 30 minutes and readings are made with the 16 mm. objective of the microscope, the light from the condenser being allowed to pass through the moist filter paper. Gentle rotation of the plates hastens the formation of large clumps of precipitate. The appearance of large clumps of precipitate indicates a positive reaction. Negative results are indicated by the absence of such clumping. Doubtful or questionable results are seldom encountered but can be eliminated by comparison with the control and a known positive. In using this technic for the first few times it is suggested that known positives and negatives be set up as controls to familiarize the worker with typical reactions.

Infrequently, though occasionally, cross reactions occur. These may be distinguished from typical positive reactions with a little experience.

There appears to be no advantage in incubation or refrigeration of the mixtures.

While the Neufeld reaction has at present largely replaced the agglutination reaction for sputum typing, the agglutination reaction has been utilized by Bullowa as a means of determining when

antipneumococcus therapeutic serum has been administered in adequate amounts.

For this procedure it is necessary to have on hand suspensions of killed pneumococci which may be secured commercially. The procedure follows:

1. Collect a drop of blood from the finger on a glass slide (or in a capillary tube from which it is later expelled on a slide).

2. Add 1 drop of the appropriate antigen suspension and mix thoroughly with a platinum loop.

3. Dry in air and immerse the slide in the following mixture: Glacial acetic acid 1 cc., formalin 5 cc., distilled water 94 cc. This both fixes the smear and also removes the hemoglobin.

4. Stain with alkaline methylene blue or dilute carbol fuchsin

Readings are made as follows:

Negative (no agglutination): —

Partial agglutination (slight): +

Partial agglutination (more marked but not complete): ±

Well marked (complete) agglutination: ++

Partial or negative agglutination is an index of insufficient serum dosage. Adequate serum dosage can be assumed when, in the presence of clinical improvement, complete agglutination occurs

In the interpretation of this reaction it must be remembered that antibody production in general does not necessarily parallel agglutinin production. It cannot therefore be relied upon without reserve

A further precaution is necessary. Because old antigen suspensions may become unduly sensitive, a control check is necessary for nonspecific agglutination (control: mixture of antigen suspension and normal saline or normal blood). If nonspecific agglutination is demonstrated the antigen is unfit for use and must be replaced by one recently prepared.

THE M AND N BLOOD GROUPS

Relationship to the Determination of Paternity

Although the application of the hereditary principles determining the distribution of the blood groups has found a rather extensive medicolegal application in Europe in the study of disputed paternity problems, the attitude of American courts has been, until rather recently, rather conservative as to their admissibility as evidence.

Since 1932, however, in view of the increasing importance given to the subject in legal as well as medical literature, American courts are somewhat more receptive to such evidence; so much so that in several States courts are now authorized by law to order such tests and similar legislation is now pending in others.

In view of these facts it is of interest to review the subject in its entirety and to present in some detail the relation of the M and N blood groups to this problem.

As everyone now knows, the ordinary blood groups (O, AB, A and B) follow in their distribution the mendelian laws of heredity and for this reason both genetic and serological principles are involved

As has been pointed out, the genetic rules employed to detect instances of illegitimacy and false accusations of paternity may be rather simply illustrated.

Thus, one may assume a theoretical population consisting of 2 clearly differentiated types, 1 dark haired (dominant), and the other fair haired (recessive)

It may further be assumed that these 2 types occur in a ratio of 60 to 40 with no intermediates. Under these circumstances the diagnosis of dark or light hair is clear and obvious

Now as there are only 3 possible mating combinations, the results must be as follows:

If both parents are dark haired about 90 per cent or more of the offspring will be dark haired, the remainder being light haired. If one parent has dark hair and the other light, 70 per cent of the offspring will be dark haired and 30 per cent light haired. When both parents are light haired—and this is the combination of greatest significance—then all the offspring must be light haired.

From these assumptions it follows that when a light haired woman accuses a light haired man of being the father of her *dark* haired child, the accusation must be false. On the other hand, should the accusation be directed toward a dark haired man positive proof of paternity could not be adduced as the property, dark hair, has an incidence of 60 per cent in the population.

The recessive (light hair) matings breed pure and, having an incidence of 40 per cent, it is possible to render a decision of nonpaternity in about 16 per cent of all false accusations.

In the same manner in the same theoretical population other individual differences can be postulated which behave in the same manner. For example, eye color, tallness and shortness, and so on. It becomes apparent, therefore, that as the number of such individual differences increase 2 conclusions are inevitable. (1) Since such differences or systems are apt to be independent, the greater their increase the greater the number of instances in which the determination of nonpaternity becomes possible. (2) Assuming a sufficiently large number of such properties they, in their various combinations and permutations, determine the individuality of the person.

Now, it is well known, of course, that, as a matter of fact, morphological prop-

TABLE 3

Parents	Children Possible	Children Not Possible
O + O	O	A, B, AB
O + A	O, A	B, AB
O + B	O, B	A, AB
A + A	O, A	B, AB
B + B	O, B	A, AB
A + B	O, A, B, AB	
O + AB	A, B	O, AB
A + AB	A, B, AB	O
B + AB	A, B, AB	O
AB + AB	A, B, AB	O

erties do not behave as simply as has been assumed above. Separation into types is never sharp and clear, and intermediate types occur. Fortunately, however, the red blood corpuscles are endowed with a number of properties (agglutinogens, etc.) which fulfill the following conditions: (a) They appear early in life, (b) they are constant throughout life, and (c) they cannot be changed by any known environmental influence. The separation of all blood into one or other of 4 groups or types depends upon the varying distribution of 2 agglutinable substances, A and B, their simultaneous presence, AB, or their absence, O.

And, as the distribution of these agglutinable substances follows the mendelian laws of heredity, their application to the determination of paternity is apparent in the same degree as in the figurative illustration given above.

The theory of heredity upon which the use of the blood types in the determination of nonpaternity is based on that proposed by Bernstein in 1924 following the extensive study of the blood groups of various races by the Hirschfelds in 1919.

According to Bernstein's theory the possible matings and possible offspring are shown in Table 3.

The validity of this table has been substantiated by investigations of thou-

TABLE 4

Gene	Genotype	Phenotype (Blood Group)
O	O O O A	O
A	A A O B	A
B	B B A B	B A B

sands of families. Any exceptions are attributable to illegitimacy.

The Bernstein theory postulates that the 4 blood groups result from the combination of any 2 of the 3 genes (the genetic unit in heredity), O, A and B residing in a particular locus in a certain pair of chromosomes. Since the homozygous* AA cannot be differentiated from their respective heterozygous† forms AO and BO, the possible combinations of these 3 genes‡ O, A and B result in 6 genotypes§ and 4 phenotypes¶ (blood types) as shown in Table 4.

As the genotype is characterized by 2 genes, 1 from each parent, the homozygous individual has identical genes from each parent (as AA or BB), while the heterozygous individuals inherit a dominant gene (A or B) from 1 parent, and a recessive gene (O) from the other parent. This results in the genotypes AO and BO.

This being so, then, in conformity with the classical mendelian ratio of 3:1 (3 of the dominant A group to 1 of the recessive O) it becomes apparent how, from a mating of 2 heterozygous A

*Homozygous pure bred, derived from like zygotes or germ cells.

†Heterozygous hybrid, formed by unlike gametes.

‡Gene A hereditary unit (factor) in the chromosome which carries the transmissible hereditary character. Also called factor.

§Genotype The fundamental hereditary combination of genes of an organism.

¶Phenotype The visible characters common to a group.

TABLE 5

Parents	AO, AO
Gene in Sperm or Egg	AA or OO
Children Genotype. . .	1 AA, 2 AO, 1 OO
Children Phenotype . . .	3 A's and 1 O

parents, children of Group O are possible as shown in Table 5.

As the sex cells carry half the number of chromosomes characteristic for the species, the sperm cells of the heterozygous A father are of 2 qualitative kinds, 1 carrying the chromosomes bearing the dominant gene (A), the other the chromosomes bearing the recessive gene (O). The heterozygous mother also has 2 qualitative sorts of ova, 1 bearing gene A, the other gene O.

Hence, as indicated in Table 3, in the combinations of 1 sperm uniting with 1 ovum, the genotype of any offspring must bear 2 genes, 1 from each parent, and it thus becomes obvious that when the dominant character A or B is absent in both parents, it cannot appear in the children of such parents.

In Bernstein's theory a parent of Group AB cannot have a child of Group O, nor can a Group O parent have children of AB group as shown in Table 6.

On the basis of these facts and following their firm establishment by extensive investigations, the use of blood groups in the determination of non-paternity was introduced into the courts in Germany in 1925. From more than 6000 cases recorded in 8 European countries a definite decision of illegitimacy or false accusation was established in 8.2 per cent (546 cases).

TABLE 6

Parents	AB, OO
Gene in Sperm or Egg	A or O
Children Genotype	B, AO
Children Phenotype	BO, A and B

TABLE 7

(The signs + and — indicate the presence or absence of agglutinations.)

Phenotype	Genotype
M + N — (M)	MM (homozygous)
N — N + (N)	NN (homozygous)
M + N + (MN)	MN (heterozygous)

It is to be remembered, first, that all those concerned (mother, child, reputed father) must be tested, and, second, that while the method can acquit, it cannot incriminate. In other words, it can never be proved by blood grouping tests that a man *is* the father of a child. It can only suggest that he *could* be. But it can definitely prove when he *cannot* be the father in a particular instance.

Moreover, while considering only blood groups, the maximum efficiency is 16 out of 100 known false accusations but the practical value of the test is only about 50 per cent of the maximum value of 16 per cent, since not all paternity accusations are false.

Nevertheless, the procedure is gaining wider and wider use in many countries, as evidenced by the growing literature on the subject recording tens of thousands of cases.

The procedure is now in use in Austria, Belgium, Germany, Czechoslovakia, Denmark, Italy, Japan, Lithuania, Norway, Sweden, Switzerland and in the Irish Free State, and is also coming into use in England.

Following the discovery by Landsteiner and Levine in 1927 of the M and N properties of blood and the demonstration that these also followed the mendelian laws of heredity in their distribution, and the still further fact that the M and N factors are independent of A and B, the application of these new factors makes possible an exclusion of paternity in 33 per cent of all instances in which false accusations are made.¹³

TABLE 8

Mating No	Types of Parents	% M Children	% N Children	% MN Children
1	M + M	100	0	0
2	N + N	0	100	0
3	M + N	0	0	100
4	M + MN	50	0	50
5	N + MN	0	50	50
6	MN + MN	25	25	50

In the case of the M and N factors, there are only 2 genes, each of equal dominance. Their combination (1 from each parent) forms 3 genotypes corresponding to 3 serologically recognizable phenotypes are shown in Table 7.

The following rules apply:

1. Unless the factor M or N is present in the blood of 1 or both parents, it cannot appear in the blood of the child (dominant rule).

2. Where both parents are homozygous for M, 100 per cent of the children are of the same type (M). The other 2 types are excluded. This holds true when both parents are homozygous for N.

3. When 1 parent is homozygous for M and the other homozygous for N, 100 per cent of the children are heterozygous type MN. The parental types are excluded.

4. When the mating is homozygous and heterozygous the parental types appear in a 50:50 ratio in the children.

5. Where both parents are heterozygous, children of all 3 types are possible in a ratio of 1M:2MN:1N.

This is the only 1 of 6 possible matings in which exclusion cannot be made.

These rules are exemplified in Table 8.

While blood grouping of the 4 familiar types is a relatively simple procedure, the detection of the M and N factors is more technically difficult and requires, as an essential prerequisite, a definite familiarity with serological principles and a definite degree of experience and skill in their practical application.

The technic in detail follows to complete the discussion.

Determination of M and N Blood Groups

Preparation of Immune Serum—

Serums are prepared by inoculation of rabbits with Group O (Moss IV) bloods previously determined to possess the M or N factors. These, obviously, must be procured from (or tested by) someone possessing specific M and N typing serum.

1. Collect at one time sufficient blood for the whole series of inoculation tests. Blood is collected in Rous' solution in which it may be preserved for many weeks

(Rous' solution: glucose, 5.4 per cent, sodium citrate 3.8 per cent; dissolve the glucose and citrate separately in distilled water; sterilize; cool and mix. Use equal volumes of Rous' solution and blood to be preserved.)

2. Wash blood 3 times in N/S and preserve cells in Rous' solution. Just before injection, wash the required amount.

3. In a series of sterile-stoppered tubes place the amounts of preserved blood required for each inoculation and place in the ice chest (Note: Wash preserved blood just prior to injection.)

(*E.g.*, First injection 8 rabbits: total 3.2 cc. divided into 8 tubes containing 0.4 cc. each.) At the time of inoculation add sufficient sterile N/S to make a convenient volume

4. Schedule of Inoculations:

Always use cells thrice washed and packed just prior to injection. Use 8 rabbits for M cells and 5 rabbits for N cells.

Inject at 4- to 5-day intervals.

1. 0.2 cc. intravenously

2. 0.3 cc. *subcutaneously* One hour later 0.2 cc. intravenously.

3. 0.3 cc. subcutaneously. One hour later 0.2 cc. intravenously.

4. 0.3 cc. subcutaneously. One hour later 0.2 cc. intravenously.

5. 0.3 cc. subcutaneously. One hour later 0.2 cc. intravenously.

Seven days after the last inoculation take a trial bleeding for absorption tests. Collect 0.5 to 1 cc. and separate serum (enough to obtain 0.2 cc. serum).

Technic of Absorption Tests:

Required: A. Washed and sedimented cells. For anti-M sera absorb with blood N; for anti-N sera, absorb with M.

B. Serum from inoculated rabbit.

C. Small test tubes, clean but not necessarily sterile.

D. Capillary pipettes: 1 cc.

E. 0.85 per cent saline (N/S).

Method for M Absorption Tests:

1. Dilute the rabbit serum 1:20 with N/S.

2. To 0.5 cc. washed and sedimented (centrifuged) cells N add 1 cc. rabbit serum 1:20, let stand at room temperature 1 hour with frequent shaking. Centrifuge and use supernatant fluid for tests.

3. With a capillary pipette place 2 drops of cell suspension in a small test tube. (Use about 6 different cell suspensions to detect differences in M (2 suspensions), N (2 suspensions), MN (2 suspensions) (including bloods used for absorption).)

4. Add 1 drop of 1:20 absorbed rabbit serum to be tested.

5. Add 1 drop of N/S.

6. Shake gently; centrifuge 1 minute at low speed. Read for agglutination by resuspending the sedimented cells.

Readings are made in terms of + to +++++; bloods N must be completely negative; otherwise high titered serums may require reabsorption or, when testing fluids are made, higher dilution of the serum is employed.

Agglutination indicates the presence of M antibody in the rabbit serum in titer according to the completeness of the agglutination.

Method for N Absorption Tests—

The technic is the same as that described above for the M absorption test, *except that all manipulations with N serum are done at 98.6° F. (37° C)*. Serum dilutions (1:20) 2 volumes (1 cc) are placed in test tubes placed in a beaker filled with warm water at 104° to 113° F. (40° to 45° C), add 1 volume (0.5 cc.) packed and washed sediment M, keep mixtures at 98.6° F. (37° C.) about 45 minutes, shake frequently, not permitting sedimentation of agglutinated cells; for centrifugation, tubes are placed in centrifuge tubes warmed and filled with water, at 104° to 113° F. (40° to 45° C.) so that water is not too cold at end of centrifuging

Tests of the Absorbed Sera for M

—1 Centrifuge all tubes (N series at 98.6° F. or 37° C.)

2 Transfer supernatant fluid to a similar series of tubes properly labeled

3 Prepare the following washed cell suspensions. M cells from 2 individuals, N cells from 2 individuals, MN cells from 2 individuals (including bloods used for absorption)

4 Set up a sufficient series of agglutination tubes to test absorbed fluids with each cell suspension

5 Dose tubes as follows (a) 2 drops of washed cell suspension (2 per cent of each of the above, 2 M, 2 N, and 2 MN suspensions). (b) 1 drop of supernatant fluid to be tested (c) 1 drop of N/S

6 Shake, and incubate N series at 98.6° F. (37° C) as above described (45 minutes).

7. Read.

Selection for Potent M and N Sera

—Now, for both M and N serums, select

the serums of highest titer and bleed the rabbit in question Then:

1. Separate the serum under sterile conditions.

2. Filter through Berkefeld.

3. Ampule or place in sterile test tubes and label.

Such serums will keep in the ice chest indefinitely

Preparation of Testing Fluids from Selected Potent Sera for Preservation—Prepare about 5 to 8 cc of several anti-M and several anti-N serums

1. Dilute serum 1:20 with N/S and absorb with one-half volume packed washed cells.

(Absorbed fluids are to be tested for specificity and potency as above)

2. Add 1 drop of toluol for each cc of absorbed fluid

3 Place in sterile, stoppered (paraffined) tubes

Testing fluids remain stable for several (4 to 6) months in the ice chest

Test of Unknown Blood —Specimens should be taken from mother, child and alleged father *Collect specimens in duplicate* and test each set on succeeding days The results should check

Test both serum and cells

1 Collect blood, preferably by venipuncture, or allow finger blood to clot. (Specimens to be mailed should be placed in a tube and allowed to clot All suspensions are made by shaking the clot with N/S.)

2 Collect also from blood library control M, N, and MN cells

3 Wash cells twice and make approximate 2 per cent cell suspensions in N/S.

4. Set up the following duplicate series of tubes: (a) Mother, (b) child, (c) alleged father; (d) M controls (2), (e) N controls (2), (f) MN controls (2).

5. Dose tubes with cell suspension as described for test of fluids (all in N series at 98.6° F. or 37° C.).

6. To one series add 1 drop of M testing fluid.

7. To the other series add 1 drop of N testing fluid at 98.6° F (37° C.).

8. Read M series after centrifuging 1 minute at *slow* speed.

9. Read N series after 45 minutes in 98.6° F. (37° C.) bath.

10. Record results.

11. Repeat tests the following day with duplicate specimens.

Both tests should check.

INTERPRETATION

Parents	Children Possible	Children Not Possible
M + M	M	N, MN
M + N	MN	M, N
M + MN	M, MN	N
N + N	N	M, MN
N + MN	N, MN	M
MN + MN	M, N, MN	

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PSYCHIATRY

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EMOTIONAL FACTORS IN HYPERTENSION

By C. SPURGEON ENGLISH, M. D.

K. A. Menninger¹ pleads for a broad point of view in approaching this disease entity. He holds that while he does not believe any disease to be purely psychogenic, he also does not believe that any disease can be accurately described as physiogenic or chemogenic. But hypertension is a condition in which not only the physical but also the psychological factors are readily recognizable, although the latter are not so easily measurable. The parallelism of blood pressure fluctuations and emotional fluctuations was one of the early physiological correlations.

Psychological study of cases of hypertension makes one impressed by the following observations:

1. The fact that transient hypertension may be induced in persons by emotional stimulation.
2. The fact that some of these cases show gross pathology of emotional status or reactions.
3. The fact that chronic hypertension may sometimes be reduced by various procedures essentially psychological in nature.

The author considers the specific emotional pathology of hypertension difficult to ascertain. To quote the author on this point, "For one thing, one must dis-

tinguish between conscious and unconscious emotional factors. It is hard enough to uncover the conscious emotional pathology of a patient and to evaluate its strength, its effect upon his total personality and upon his vascular tension in particular. It can be done, usually, if one has the patience to listen to what the patient has to say. But it is still harder to get at the unconscious emotional factors, those which the patient cannot tell us about even if he would. This requires the psychoanalytic technique, and, therefore, a great amount of time.

"It is very hard, too, to separate the emotional factors stimulated by the physician himself and by the whole program of examination and treatment from those more continuously operative. Again, even when one discovers and evaluates the emotional factors in a particular case quite definitely, it is exceedingly difficult to show except by deductive hypothesis just how or how much these things affect the blood pressure. It is impossibly absurd, for example, for a psychoanalyst who is listening quietly to a patient who, with sobs and tears, is confessing some poignant source of anxiety, to interrupt this by leaping from his chair to seize and apply a sphygmomanometer. Or consider this complication. I was conversing with a patient with very severe hypertension while an assistant took blood pressure readings regularly every 2 minutes. The patient had voluntarily renounced smoking after many years of heavy addiction. I proposed that we observe the effects of smoking a cigarette and he willingly co-operated. My assistant redoubled his efforts to make accurate consecutive readings. While we were waiting for the cigarette 'to take effect,' my patient suddenly remembered a distressing occurrence which had taken place in his home the previous week and

began to relate it in detail. His systolic blood pressure rose 30 mm. of mercury but whether from the cigarette or from the recollection, who can say?"

Nevertheless, he felt he was able to make some deductions concerning the personality of patients with hypertension which happened to correspond fairly well with other workers on the same problem. "They indicate that patients with hypertension are characterized by an external poise, often gentleness and amiability, beneath which there exists a strong undercurrent of fear which arises from the existence of strongly repressed aggressions, usually dependent upon resentment over threats to the patient's dependent security."

Some clinical cases are cited of which the 2 following are taken at random.

"An old maid for 30 years had been the trusted private secretary of the executive head of a large business. Apparently he had supreme confidence in her and was absent from his office weeks and even months at a time. Much as she appreciated this confidence, however, and great as her admiration and respect for her employer were, she was exceedingly distressed by the growing rebellion of factions in the business which threatened to overthrow his control of it, and, incidentally, remove her from her position. When she would appeal to him to return and assume the responsibility of controlling the business, he would reply that he had confidence that she would do the right thing. This she felt totally unequal to, but never a word of criticism or reproach of her employer would pass her lips even in the intimacies of a professional consultation. This repression and psychic tension was associated with a high degree of arterial hypertension.

"A married woman of 51, with a blood pressure averaging 183/104 and with occasional readings much higher,

had a fairly characteristic psychological picture. She was an exceedingly gracious and dignified, composed person, amiable at all times under the varied experiences of a complete psychiatric examination. For 10 years she had been the executive head of a large international organization and had traveled extensively in Europe, Asia, and all parts of this country making addresses at large and small meetings. She was married to a physician 20 years her senior. Two years prior to the discovery of her hypertension he had been removed from a position which he had held for many years and was attempting to make a living for his wife and himself by the re-establishment of a private practice. Progressive loss of vision made this still more difficult. The frequent public appearances which his wife was obliged to make in connection with her work required an expenditure for clothes at a time when it was even difficult to buy sufficient food. This financial restriction in conjunction with her pride and the necessity for making a good appearance before her townspeople and her organization was an increasing source of conscious anxiety to her as was also the increasing age and anticipated helplessness of her husband. As she was discussing this latter point her systolic blood pressure mounted to 238 mm. Consciously, of course, it would have been absurd for her to blame her husband for their predicament but the unconscious is not guided by any such rules of justice or fair-mindedness. Hence her hostility was repressed, the inner psychological tension paralleled the high arterial tension."

The work of an internist, David Ayman, of Boston, is quoted as that of a nonpsychiatric observer who considers psychological factors of treatment extremely important. "Ayman was impressed by the widely varying reports

of the successful treatment of essential hypertension by many different drugs and methods. He carefully analyzed 35 research projects of this type and discovered that in practically every article complete or partial symptomatic relief was reported in spite of the enormous range of treatment methods. He noted, also, that complete failure was seldom reported. He concluded that there must be some common factor associated with the administration of these various treatments which was not recognized by the experimentors, and as a research project studied the effect of the administration of a placebo (dilute hydrochloric acid). As minimal criteria of a diagnosis of essential hypertension he insisted that the patient should have had at least 5 abnormally high readings of blood pressure and that they should have been observed for at least 2 months prior to the beginning of treatment. An otherwise unselected group of 40 patients was then treated and followed. Thirty-three of the 40 patients showed definite improvement, *i e.* the treatment was 82 per cent successful. The symptoms were relieved and the blood pressure fell, however, with a considerable disparity in the parallelism of the 2 factors.

"Ayman was convinced that the common element in the treatment to which the patients responded with so much benefit was that of 'the enthusiastic giving or doing something for the patient'. His point is that *treatment*, regardless of its nature, benefits the hypertensive patient."

The author feels that in the treatment of these cases "some emotional experience takes place which lessens the symptoms and the tension and presumably this is brought about by a lessening of some inner tension which the patient unconsciously maintains." Moreover, that despite the potassium-calcium ratio, or the

kidney changes, or the arteriosclerosis, there remains behind these observations emotional factors which act as a co-ordinating determinant.

From the practical management of cases of hypertension 2 practical suggestions are emphasized as psychologically sound. The first of these is to give the patient a quiet, noncritical, sympathetic audience in which he is en-

couraged to relieve emotional tension. For either patient or physician to focus too much attention upon the manometric readings is to be avoided.

The second practical suggestion is to avoid rest cures in previously active people, but instead to advocate reasonably mild exercise and continued work and regard the forbidding of these things as the greater hazard.

FEEBLE-MINDEDNESS

By ROBERT A. MATTHEWS, M.D.

Social Status—C. P. Sheldon and L. H. Ziegler² point out that among average or superior members of society, marriage presupposes adaptations and creates problems of a varied nature. It is difficult for all these to be satisfactorily resolved, even with every aid that can be brought to bear on them. In the case of handicapped persons who marry, the problems that ensue are no less numerous or complicated. But among the feeble-minded the awareness of such problems, by the nature of the circumstances, is relatively defective, and the burden of solution must be assumed largely by others in society more capable of bearing them.

The authors have made a study of 50 unselected married patients seen in a free antepartum clinic over a period of about 4 months. The Stanford revision of the Simon-Binet test was given to these patients by an experienced psychologist. They found that 22 per cent of the patients were feeble-minded, which is a far greater percentage than is to be found in the general population and point out that in reality these patients participated in a form of child marriage, usually with governmental and religious sanction, that constitutes a more haz-

ardous factor to society than the occasional child marriages so much publicized recently. Intelligence quotients were plotted against age at marriage and indicated the lower the intelligence quotient, the earlier the individuals tended to marry. From their observations it seemed clear to the authors that feeble-minded above the grade of idiot may marry without much restraint even in States that have laws disqualifying them. The feeble-minded tend to marry earlier than normal adults and apparently procreate more rapidly.

Laws pertaining to the marriage of defective individuals are inadequate or poorly enforced. Laws not infrequently mention idiocy (mental age 0 to 3 years) as a condition disqualifying for marriage but few, if any, idiots are capable of attempting to contract marriage or to reproduce. Arrests of psychic development above this level (imbecility, with mental ages 3 to 7, and moronism, with mental ages 7 to 12) are frequently not mentioned in marriage-disqualifying laws. Most of such defectives are by nature incapable of, and irresponsible for, making contracts such as marriage. Since they often appear to be normal adults, but in reality are mere children, they

are taken advantage of and exploited. In difficult times and in environments where they are not understood (and they usually are not) there is little recourse for many of them except in delinquency, relief rolls, or starvation

Governments have not attached sufficient importance to the age at which intellectual growth ceases; this is of much greater significance than the actual age of the person. If one examines the inmates of prisons, almshouses or reformatories, people on relief rolls, or women who give birth to children out of wedlock, one finds that a far larger percentage of persons is included whose psychic arrest has occurred in childhood than is found in the population as a whole.

Sterilization as a means of removing some of the feeble-minded from the race is suggested as one method of dealing with the problem as well as segregation and registration of these individuals. With adequate registration, laws disqualifying for feeble-minded marriages might be more effectually enforced.

The expenditures incurred in the United States by allowing the feeble-minded to live as they wish, with palliative assistance, has perhaps been one of the heavy prices we have paid for what we call personal freedom. We are at the threshold of a reappraisal of the liabilities and the assets involved which can come about through a broadened interest in the public health. If individual liberty is lost when one has smallpox or leprosy, it would seem that the chronic disease feeble-mindedness might be controlled in the interest not only of the patients themselves but for the health, economy and safety of the public as well.

Doll and Longwell,³ in an article entitled "Social Competence of Feeble-minded in Family Care," point out that the idea of permanent institutional cus-

tody for the feeble-minded has definitely been modified by the experiences of the past quarter century. We now see that only a small fraction of all the feeble-minded ever reach institutions and that for those who do so lifetime segregation is not always imperative. The majority of them continue to live in their own families and get along somehow in the community. From an economic standpoint it would not seem practical to build sufficient institutions to house 1 per cent of our national population as feeble-minded, a percentage which is generally considered a conservative estimate.

Other influences besides the feeble-mindedness itself may be the reason for commitment and if these precipitating causes such as misconduct, broken homes, inadequate community resources and the like are ameliorated, it may be possible to provide suitable families, permitting the home care of certain patients. In order to do this a study of the foster parents, utilizing the Vineland Social Maturity Scale in measuring the social competence of persons into whose custody the patients will be placed, has been attempted. The results of their study have been summarized in the following propositions:

- 1 Family care is a desirable part of any program for the social supervision of the feeble-minded.

- 2 In this study postinstitutional family care has been evaluated in terms of a successful program now in operation at the Newark, New York, State School.

- 3 The social competence of the foster parents in whose family care these patients were placed was slightly but definitely above the average of the adult sample on whom the social scale was standardized.

- 4 Adult female patients placed in family care were found to be generally of imbecile grade, but included some

idiots, some morons, and some patients of all grades with serious physical handicaps. These patients were well, adjusted and happy in the family care environment; they were also useful but not exploited in these homes.

5. The problem of finding suitable homes is one of no mean proportion, but the success at Newark demonstrates the feasibility of doing so. Those who think it cannot be done may well be advised to go to Newark and see it being done.

The Social Cost of the Feeble-minded Family⁴—Two studies of the cost to society of the feeble-minded family have recently been published. The first study was made by the welfare bureau of a city in western Germany. It traces the cost to society since the year 1880 of a certain defective family. Eighty members of this family received a total of 201 sentences for various offenses, 19 children were committed to special industrial schools, 10 members of the family were prostitutes. This family had cost the community a total of 205,000 reichsmarks, a sum that corresponds roughly to the amount of taxes paid by 10,000 workers or to the expense of erecting 68 workers' colony homes. The second investigation took place at Stuttgart. A manservant begot 7 feeble-minded children in wedlock. After his death the feeble-minded widow had an illegitimate child likewise feeble-minded. All 8 of these children, completely neglected, had to be placed in institutions for the feeble-minded. In 10 years the State has expended 37,087 reichsmarks for their care. If each child's further expectation of life is estimated at 30 years, the future cost to society will be 100,000 reichsmarks.

Mongolism—An editorial⁵ summarizes the findings of A. Bleyer's⁶ article dealing with the rôle of advanced maternal age in causing mongolism.

In spite of the antiquity of mongolism as a medical subject, its causation has remained obscure. Bleyer has recently analyzed its incidence in relation to advanced maternal age, low fecundity among women bearing children with mongolism, prolonged interval preceding the birth of a mongoloid imbecile, maternal reproductive exhaustion, ultimogeniture and paternal reproductive exhaustion. He concluded from these studies that the rôle of advanced maternal age in causing mongolism is undeniable. Although the peak maternal age in the general population in this country in 1934 was 24, the peak age of mothers producing mongoloids in his series of 2822 cases was 41. Furthermore, the incidence of mongolism increases steadily through the childbearing period. The likelihood of producing a mongoloid imbecile is increased in direct proportion to the number of menstrual cycles through which a woman has passed. Of the entire group of 2822 mongoloid imbeciles, 900 were born to women under 31 years of age and 1922 to women over 31. Mothers from 15 to 19 years of age produced 3.4 per cent of the mongoloid imbeciles, or only one-fourth the expectancy when judged by their proportionate contribution to the total births. In the years from 35 to 39, the mothers produced only 0.9 per cent of the births in the general population gave birth to 23.8 per cent of the mongoloid imbeciles, or an excess over expectancy of 25 to 1. The succeeding 5-year period, from 40 to 44, showed a further increase above expectancy of 75 to 1. No satisfactory evidence could be found of the relationship to the etiology of mongolism of the other factors investigated. Probably the apparent relation of any of these factors to mongolism can be explained simply through the admixture of advanced maternal age.

Kehrer⁷ describes 4 cases of mongolism in newborn infants and 1 of the extremely rare cases of familial mongolism. The manifestations of the developmental disturbances in the brain are already so pronounced in the newborn infants that a diagnosis is possible without difficulty. In addition to the more or less characteristic facial expression, the following symptoms are of diagnostic significance: General muscular hypotonia, cutis laxa which is present chiefly on the occiput and on the back of the neck, immobility, somnolence and apathy, and the shortness and inward curvature of the terminal phalanges of the fifth fingers (Siegert's sign). The diencephalic adenohypophyseal system may be involved in the developmental anomaly of the brain. This results in edocrinopathies which may exist at birth but which do not become manifest until later. The observation of some authors that mongoloid children are usually borne by mothers who have passed the age of 40 was corroborated in only 1 of the 4 newborn. The author thinks that mongolism is caused partly by impairment of the germ plasma (ovum or spermatozoon), partly by damage to the embryo. In 1 of the 4 cases the mother had passed through an epidemic encephalitis 2 years before the birth of the child. In another case, consanguinity in the distant ancestry may have played a part.

Benda⁸ in a study of the endocrine pathology of mongoloid deficiency examined the thyroid glands of 20 mongoloids which she found to be different from the normal. Microscopically the pathology in mongoloids is thought to be rather definite and characteristic, the changes appearing to be indicative of pituitary disorder. During the first months of life the thyroid shows an increase in parenchymatous growth without formation of secretory vesicles. The

size of the tubules which are to be found varies markedly. Besides small tubules without colloid, are other vesicles in which an increase in size is noticeable. The epithelial walls show small, pyknotic nuclei which are rich in chromatin and aside from the walls there is an irregular growth of epithelium. The connective tissue is increased. This conception led the author to make a study of the pituitary body, 14 glands being available for microscopic examination. The material was controlled by the study of the glands from 50 cases of children who died of other diseases. The study of the pituitary revealed interesting pathology.

In mongolism, a marked increase in acidophils is recognizable, but what was considered more important in the first years of life there is a rather complete lack of basophils to be found. In 6 instances basophils were completely lacking. In cases in which few basophils were present, their type is always immature. The same condition was not found in any other type of disease and it was concluded that alterations of the basophilic system are so invariably associated with mongolism that these findings may be considered as typical of the mongoloid pituitary. Although in mongolism there is an amazing variety of disturbances of the endocrine system to be found, there are many indications that the alterations of the pituitary body are the primary causes of such a general disorder.

Myers,⁹ in a paper dealing with the etiology of mongolism, considers the evidence from previous studies to warrant the conclusion that mongolism is dependent on certain environmental conditions which are effective at about the time of conception and which are probably endocrine in nature.

In his discussion the author states that although maternal hyperthyroidism is not, by itself, the adequate cause, it may well be one of the more prominent symptoms of that particular but complex endocrine disturbance which is responsible for the occurrence of mongolism

Etiology—Bonn University's Institute of Hygiene¹⁰ in collaboration with the municipal health department has investigated the relationship of alcoholism to feeble-mindedness and defective heredity. Dr Lechner found that of 254 pupils in the special schools for backward children 205 (80.7 per cent) were congenitally tainted. The accompanying table lists the familial defects established and the percental distribution of these among the 205 children studied.

Lechner's observations show that, in addition to a computation and evaluation of the incidence of defective heredity as a whole, one should also attempt a more intensive social-medical study of particular hereditary defects. Lechner divides hereditary taints into 2 categories on the basis of the foregoing data:

1. Two-thirds of the children examined are victims of the will to procreate on the part of mentally or neurologically subnormal parents.

2. Furthermore, in the ascendancy of from one-fourth to one-third of the children, at least 1 parent or grandparent was established who, on account of addiction to alcohol, must have been morally or physically unfit to have issue.

These observations clearly show that the hereditary taint of feeble-mindedness cannot be eradicated solely by sterilization of mentally subnormal persons. Misuse of alcohol plays an important part with regard to the mentality of the offspring, all the more so since students of medicosocial problems the world over have found that persons who overindulge in alcohol are the very ones who, pro-

vided they are sexually active, tend to propagate far more rapidly than temperate persons and even more rapidly than the feeble-minded. The foregoing statement applies above all to those habitual heavy drinkers who exhibit no signs of "alcoholism" in the forensic sense of the term. Thus is posed an important problem, one which is not to be solved by eugenic legislation alone, since entirely new cases of alcoholism will continue to originate.

DEFECTIVE FAMILIAL BACKGROUND

	Percentage
Both parents of extremely low intelligence	4.1
Father alone feeble-minded	5.9
Mother alone feeble-minded	17.2
Parents of subnormal intelligence	21.3
Feeble-mindedness in ascendancy but not in parents	3.0
Feeble-minded siblings	6.5
Epilepsy	8.3
Other mental defects of parents	1.8
Alcoholism of parents and grandparents	29.0
Syphilis	2.3

Pollock and Levene¹¹ have made a study of hypophyseal influence on cranial structure with relation to mental development. The study was undertaken with the purpose of ascertaining the relationship of intelligence to physical changes in the skull as revealed by roentgenologic examination, the material consisting of microcephalic idiots and morons from 3 State schools for feeble-minded and of students from 2 colleges. Among the latter some examined were in the lower third of their respective classes and some were on the honor roll. The authors are of the opinion that at present it may be within the realm of possibility that the recognition of abnormal pituitary states in infancy by roentgenograms of the skull may afford early opportunity for substitution therapy and thus alter the course of a predestined

mental deficiency. They come to the conclusion that the functional activity of the anterior lobe of the hypophysis is recorded in the architectural variations of the skull. Study of these changes in small groups of various mental levels suggests an apparent correlation of anterior lobe activity with mental development.

Sterilization—Arnold¹² gives a brief review of the first thousand patients eugenically sterilized at the State Colony for Epileptics and Feeble-minded (Va.) since the sterilization law was passed on March 20, 1924, by that State and points out that the constitutionality of this law was upheld by the United States Supreme Court in a famous decision handed down by Mr. Justice Holmes on May 2, 1927. The author's conclusions are that heredity and environment both play an important part in the production of feeble-minded persons, that when both heredity and environment are bad, there is only a very remote possibility that the child born in those circumstances will develop into a normal adult. From the figures that are compiled it would appear that feeble-mindedness is inherited in the direct line; epilepsy more often in the collateral; that while the feeble-minded beget feeble-minded all too often, the epileptics do not beget epileptics to any great extent but they do beget defective children whose deficiency is not of a convulsive nature.

The author believes that eugenic sterilization has clearly proven its value in that by means of it we have been able to place in their own or foster homes some 632 of 1000 patients sterilized, and have thereby relieved the State of Virginia of the burden of their care and support.

It is hoped, by means of the present system of careful selection, it will be possible to place satisfactorily a much

greater proportion of the next thousand patients sterilized at the State Colony.

The Psychoses with Mental Deficiency—Pearson¹³ studied the major syndromes seen in a group of psychotic mentally defective women and has reviewed the case histories of 150 patients and presents a summary of the material from several records as illustrative of the entire group. He considers his series of cases to be representative of the clinical material commonly considered in the heterogeneous group of cases diagnosed: psychosis with mental deficiency. In idiots and at times among imbeciles and morons he found psychosis of the organic reaction type, the disorder being a total disability on a physiological level characterized by gross disorderly conduct, impersonal and nonadaptive. On the other hand, in morons and imbeciles but probably not among idiots he observed both total and partial personal adaptive reactions such as benign excitements, depressions and psychoneurotic ways of thinking and blundering through life. In those psychoses where the chief feature is the disorder of mood, the prognosis is good for recovery from the psychosis. Where splitting-of-the-personality symptoms are prominent, the prognosis is difficult to determine. It seems that the original inferior endowment may have some protective value, in that the personality does not split so far asunder or that resolution takes place more easily than in (intellectually) normal people. The psychoses are atypical. So are the recoveries. One sees many mentally defective persons passing through what appears to be irreversible hallucinatory-delusional states yet recovering without any particular residue. It does seem that intelligence is not quite necessary for the production of a particular mental state, for careful examination shows the same mechanism at

work in the imbecile as in the highly intelligent, allowing for certain differences attributable to the substrata.

Treatment—In an article dealing with the care and treatment of cerebral palsies, W. M. Phelps¹⁴ discusses the problem in a comprehensive manner, pointing out that the mental level of the individual must be determined as nearly as possible. The mental age of the child must be determined by the Binet or some similar scale but this is not the only age which must be measured in the child handicapped from birth as it is impossible to determine exactly what limitations the complicated handicap may impose. The child must be measured physically, so that the percentage of the ability to move at a given age as compared to that of the normal child will be known. He should also be measured from the point of view of his social competence and his emotional age should be determined as far as possible since the centers controlling the affective life of the individual may be involved. Often the true underlying situation can be determined only by a test of teaching, if the child can be made to progress and learn at the rate of year per year, then obviously true mental deficiency is not present, instead, the ability to learn by the usual methods is blocked by some part of the handicap and special teaching methods are necessary.

In these cases it is necessary to distinguish between spasticity and athetosis. If a pyramidal condition, or true spasticity, is present there should be hyperactive knee and ankle jerks, a positive Babinski sign, occasionally ankle clonus, diminished or absent cremasteric and abdominal reflexes and hyperactive biceps, triceps and periosteal reflexes. In the case of athetosis or an extrapyramidal disturbance of any kind the reflexes should be essentially normal.

However, a Babinski sign may be present at times. When there is speech involvement with spasticity the defect is rather uniform. In the athetoid patient in whom involuntary motion is the primary difficulty, the speech is upset by the involuntary motion of the tongue. The words never come out distorted in the same way but on repetition are spoken a different way each time. In treating the athetoid child it is necessary to keep in mind that he reacts to his involuntary motion by voluntary tension and after a number of years the tension habits become so fixed that he cannot make any motion without bringing in extreme stiffness. His habits must be unlearned in order to bring about a diminution of the athetosis. No amount of repetition will do any good unless attention is first given to relaxation. The general nature of the problem in these cases is complicated. A program must be arranged in which there is a correlation between the orthopedist, the pediatrician, the neurologist and the physical therapist, and psychologic aid is necessary in adjusting these children and their behavior to the world at large.

Delinquency Doll and Fitch¹⁵ in an article dealing with the social competence of delinquent boys state that scientific study of the individual delinquent and of juvenile delinquents as a class has revealed a number of conclusions some of which may be noted as follows:

- 1 The delinquent typically comes from an underprivileged environment
- 2 He is typically of dull-normal intelligence, bordering on high-grade mental deficiency
- 3 His intelligence and his educational attainments show relatively greater retardation in verbal intelligence than in nonverbal aptitudes
- 4 He is typically untrustworthy
- 5 He is typically in need of sympathetic social control, especially during his adolescent years.

These observations are generally summed up in the conclusion that the delinquent is a socially inadequate person but this has never been expressed in a single measure of social competence.

Employing the Vineland Social Maturity Scale in a study of 91 juvenile delinquents, it was discovered that in the group studied which was taken as representative, the social competence of the delinquents is strikingly below that of normal nondelinquents, being principally in the feeble-minded and borderline ranges of social competence.

L. A. Lurie¹⁶ in a paper covering endocrinology and the understanding and treatment of the exceptional child states that an analysis of the first 1000 cases of behavior disorders in children studied at the Child Guidance Home in Cincinnati showed that endocrine disturbances of various types and degrees of severity were present in approximately 20 per cent. In approximately 10 per cent of the cases, the glandular disturbances were the principal causative factors.

In addition to the direct effects of the glandular disturbances indirect effects include the mental attitude adopted by the child toward the physical abnormality. This often produces emotional conflicts of great severity. A clinical syndrome in which extreme motor restlessness, destructiveness and speech disturbances are outstanding symptoms is mentioned. This triad of symptoms when present in some children almost always indicates a state of hypothyroidism. The child is very restless—often the restlessness is so marked he has to be forcibly restrained. He is careless with his possessions to the point of destructiveness. The complaint, however, for which most often the physician is consulted is that he shows some form of speech involvement, an involvement that may range from inability to pronounce certain letters and sounds to

speech blocking and even to complete inability to speak. These patients respond readily to thyroid medication. The rôle of pituitary disorders in the production of behavior disorders is discussed by the author, who cites several authorities on the subject.

Oxycephaly—J. E. J. King¹⁷ describes a new operation for the relief of oxycephaly which is thought to be due to premature closure and obliteration of the cranial suture lines. In these cases the sutures of the skull have been prematurely closed, fused and obliterated at a period of life sufficiently early to prevent full growth or development of the brain. This results in the following changes: (a) Headaches in a number of instances, which may take place at such an early age that they are not recognized; (b) convolutional markings and thinning of the skull, which are readily recognized on roentgenograms; (c) unusual and abnormal irregularities of the skull, due to the fact that the skull is held rigid in some positions and gives way behind the increased intracranial pressure; (d) increase in intracranial pressure, as shown by measurement of the intraventricular pressure and diminution in the size of the ventricles; (e) marked bilateral exophthalmos which may be so extreme and prolonged that loss of the eyes may ensue, and (f) early bilateral papilledema followed by atrophy of the optic nerves, resulting in failing vision or blindness.

The author discusses the advantages and disadvantages of the operative approaches previously advocated and proposes a new operation to be performed in 2 stages, consisting of making a "mosaic" of the cranial vault. A case of typical oxycephaly associated with extreme exophthalmos, increased intracranial pressure and failing vision in which

the operation was performed successfully is described in a preliminary report. Following the operation, the previous apathetic appearance of the patient had changed to one of alertness, vision which was originally so poor that the patient

could see only about the bed had improved so much that he could recognize individuals at a distance of 100 feet or more and the child was able to take an active part in the children's play in the ward

MANIC-DEPRESSIVE PSYCHOSES

By JAMES A. FLAHERTY, M.D.

Although the major emphasis of hypoglycemic and convulsive therapy has been directed to dementia precox, the extra-schizophrenic application of these methods has received considerable attention during the past year (1938). **Insulin therapy** has been found to contract the duration of attacks of manic-depressive depressions and has been reported to have an ameliorating effect upon the manic phase of the psychosis. Strecker, Alpers, Flaherty and Hughes¹⁸ report favorable results in the manic phase with **convulsive therapy**. Singer¹⁹ has reported very favorable results with **metrazol** in manic attacks and contrasts its greater effectiveness with **narcosis therapy**. Bennett²⁰ observed encouraging results in the older age group, whose agitated and depressive symptoms had not responded to hematoporphyrin, fever therapy, narcosis or appropriate endocrine treatment. Menninger²¹ reports his belief that convulsive therapy may be more effectual in depressions than in schizophrenia.

Injury of the thoracic spine incident to metrazol convulsions has not been sufficiently studied to evaluate its remote sequelae. It should be considered

as a possible complication. However, when this form of therapy is elected, recent observations have shown compression fractures in a high percentage of cases. Paradoxically, the most severe roentgenological damage is often clinically asymptomatic. No neurological damage is reported.

More recently, the work of Himwich, Alexander and Lipetz on the effect of **nitrogen inhalations** on the course of schizophrenia, suggests that this method of treatment will probably be extended to the manic-depressive psychoses. Although too little is as yet known of the by-effects of nitrogen inhalation, it would seem to be superior to metrazol convulsions because of its second to second control and because it excites no negative disposition to treatment in patients. Their work was inspired by the observation that the beneficial effects of metrazol are derived from the depression of cerebral metabolism. In nitrogen therapy, oxygen saturations as low as 15 per cent are reported by Himwich and his coworkers, contrasted with metrazol therapy, in which the oxygen saturation attains no lower level than 40 per cent.²²

ORGANIC MENTAL CONDITIONS

By JOSEPH HUGHES, M.D.

Mental Symptoms Associated with Brain Tumor²³

While there were no symptoms specific for brain tumor, 77 per cent of 530 patients with expanding intracranial lesions showed mental symptoms. Supratentorial tumors gave mental symptoms twice as frequently as infratentorial tumors.

When the tumor involves both hemispheres, the most severe and varied type of psychic disturbances are found. This is also true for very rapidly growing tumors, because of the sudden appearance of intracranial hypertension.

It is stressed that the mental symptoms do not always present the characteristics of the so-called organic reaction type. The mental picture includes changes in affect, in intellect and of higher psychic functions. Visual, auditory and tactile hallucinations are frequent.

Delirium Tremens²⁴

Clinical Evaluation of Use of Fluids in Treatment—In treating 150 cases of delirium tremens with restricted fluids, 1000 cc. in 24 hours and 150 cases with forced fluids, 3000 to 4000 cc. in 24 hours, Piker had a mortality of about 5 per cent in both groups.

When fluids were forced, there was more likely to be a stormier course. The average hospital stay in both groups was approximately 4½ days. Piker feels that fluids should be forced in those cases in which the patient has a coincident morbid rise in temperature.

Hydrotherapy²⁵—A course of treatment of 112 cases of delirium tremens consisting of cold wet packs during periods of excitement and active hallucinosis, neutral baths of 96° F. (35.5° C.),

cabinet baths, needle spray and saline cathartics, resulted in recovery in 107 patients. The results obtained with this type of treatment are comparable with other series of cases treated by other methods, death occurring in about 5 per cent of cases.

Vitamin C Content of Cerebrospinal Fluid in Nervous Disorders²⁶

Vitamin C studies of 12 patients with nervous disorders failed to give any relationship between a diffuse anatomically demonstrable impairment of the brain and vitamin C elimination. The vitamin C content of the spinal fluid was reduced in epilepsy, tabes, paresis, and cerebroarteriosclerosis.

Mental Symptoms of Pellagra²⁷

Spies and his associates found that patients with subclinical pellagra commonly have complaints of a neurasthenic nature, such as fatigue, anorexia, vertigo, insomnia, palpitation, feelings of unrest and anxiety, apprehension and distractibility. Symptoms of an acute psychosis were observed in 60 pellagrins. The mental symptoms of pellagra responded to treatment with adequate amounts of nicotinic acid. It is recommended that patients with severe mental symptoms receive at least 500 mg. of nicotinic acid daily, preferably in 10 divided doses. Extremely severe cases should be given 1000 mg. Treatment of patients with subclinical and mild pellagra with nicotinic acid will prevent the development of mental symptoms.

Results of Malarial Therapy in Neurosyphilis²⁸

Fifty-five per cent of 190 cases of cerebrospinal syphilis given malaria showed

improvement or complete remission as contrasted with 30 per cent improvement in another group receiving only chemotherapy. (Infection with the quartan parasite is recommended.) Patients under 30 responded better than older patients. Those with organic signs responded very favorably to treatment. The goal in therapy recommended is to give a patient a course of 21 paroxysms which reach a fever of 104° F. (40.0° C.) or higher

Dementia Paralytica²⁹

Clinical and Therapeutic Experiences—A clinical study of 295 cases of dementia paralytica revealed more than 50 per cent were expansive, 8 per cent were euphoric, 3 per cent were depressed, and 3 per cent paranoid. *Malarial therapy* is the treatment of choice. Five years should elapse before making a final estimate of its effectiveness.

Cerebral Palsies¹⁴

Care and Treatment—Phelps recommends as the first step in the treatment of cerebral birth palsies, careful evaluation of child's mental age, measurement of child's social age, and of his emotional age as far as possible, preliminary to any corrective measures.

The child must also be measured physically in regards to his ability to move. The plan then is to fit the training to his mental and physical ability, taking care to differentiate between true mental deficiency and retardation on the basis of physical handicap. According to

Phelps, the percentage of children with a birth palsy who are mentally normal but are suffering from retardation due to the handicap of their condition is apparently greater than the actual numbers of feeble-minded.

From the physical standpoint, the athetoid child should be taught relaxation, the spastic child should be given alternation exercises of the legs. In case of spasticity of both legs and arms, it is important to first stress the development of the proper use of the arms, later the legs. If speech is affected, it is important to try to establish this function early so that the child can communicate with those around him.

In general, all training should be individualized in regard to each child's special needs. Special training should start early. Speech work should be carried on between the ages of 2 and 5 years. Gross motor co-ordination involving the large joints should be started in the first year; fine co-ordinated movements at the fifth year. If walking is to be attempted it should be done at the preschool age. Care should be exercised as to establishing good behavior. These children should be trained early to be much more responsive to discipline than normal children, as they must develop the willingness and obedience to enable them to carry out necessary corrective measures.

All the above applies in particular to the child who is not mentally deficient, but to the one who is retarded because of his physical difficulty.

PSYCHOANALYSIS

By O. SPURGEON ENGLISH, M.D.

Leon J. Saul³⁰ points out that "the terms 'common cold' and 'common sore throat' are rather vague and probably describe a variety of conditions which

display a similar symptomatology. The essential feature is probably the congestion with catarrhal secretion of the upper respiratory mucosae, especially of the

erectile tissue in the nose. That an infectious agent, a filtrable virus, may play an etiological rôle is apparently established, particularly by experimental work in the laboratories of Dochez, Doull, Long, and others. But in many cases other factors seem to be of predominant importance; for example, unusual exposure, sharp changes of temperature, chemical irritants and allergic conditions. That in certain instances emotional disturbances may play a rôle has also been recognized. The present observations are concerned with this emotional factor and that in certain cases it may be the most prominent feature in precipitating the symptoms of the 'common cold' and sore throat."

The statistical data reveal that "of 60 patients in the practice of 6 different physicians, 15 had been subject to unusually frequent colds and sore throats before coming to analysis. But in the average period of 3 years since completing their analyses, every one of these patients has been either free from colds or has had them with conspicuous rarity. No other treatment was employed by any of the patients. They came to analysis because of emotional difficulties. The colds were in every case purely incidental. The series is small, and *post hoc* does not mean *propter hoc*. But the regularity with which relief from colds is seen to follow the resolution of emotional difficulties, without other treatment, is a significant indication that emotional factors can play an important rôle in the etiology of certain colds, and that they do so in an appreciable percentage of cases."

Some of the clinical findings in his cases were as follows. In the analysis of a middle-aged man, it developed that he was a markedly passive character which had resulted from "spoiling" in childhood by an overindulgent mother. This

passivity was, of course, unconscious and to keep it concealed the patient made a great show of independence. However, as the analysis proceeded these passive tendencies began to reveal themselves through dreams of being fed while the patient slept upon his back and breathed through his mouth. When in his daily life his expectations of receiving what he wanted from others he reacted with oral-sadistic dreams accompanied by severe grinding of the teeth, first noted by his wife. As a result of these activities, his throat, gums and jaws would be sore in the morning. Also it was noted that at the time some of his desires were thwarted, he would react with nasal congestion and secretion. If thwarting were severe enough there would be coryza, mild depression, nausea, constipation, headache and fatigue. This gave the picture of a cold and sore throat with constitutional reaction. But all these symptoms began to disappear almost immediately following a burst of insight into the passive receptive demands and the rage at thwarting. They would be gone within a day. For 2 years since the analysis there have been no winter colds, something which the patient had never experienced before. Moreover, he has been free of a mild soreness of the pharynx just behind the soft palate which had been persistent for many years.

The second patient was a very talkative girl in the middle twenties who came to analysis because of her inability to eat in public, especially when she was with an attractive young man, and because of a mild leukorrhea (diagnosed by her gynecologist as catarrhal vaginitis). The patient was one of many children in a very poor, but proud, family. The father, after spoiling the children in their early years, later withdrew all interest in the family and ceased to contribute to its

support. With deep, almost conscious anger at the father, the patient turned from him to regressive oral attachment to her mother. Out of generosity and loyalty, she repressed her strong, always unsatisfied receptive desires; she tried cheerfully to share alike and, even at an early age, to work and contribute to the family. But the old desires, intensified by repression and thwarting, persisted, although she could not admit them consciously because of her guilt about them as "selfish."

The clinical material in this case has similarities to the former, "she expressed her envy of her sister's engagement and said that on the preceding evening she had felt a tickling in her throat, all night she dreamed she was swallowing, or else was really swallowing, and this morning her throat was sore. She then expressed her anger at the dentist because, arriving at his office, she had found 2 women waiting there ahead of her. She deprecated them as well as him."

The next hour she said that for the past 2 months her jaws had cracked loudly when eating and that she sometimes had difficulty in opening her mouth 'on one side or the other.' Such was the case this morning and besides she awoke with a cold (coryza, stuffy head, postnasal secretions, fatigue) and sore throat. Anger at oral thwarting followed—as, for example, at a girl serving the patient's sister a poor meal. Constipation appeared at this time. In the next hours she brought masochistically colored associations designed to hide her guilt in connection with her oral and genital receptive demands (always combined, as drinking with men, an attractive man selling sandwiches, etc.) and also in connection with her anger at the receptive thwarting. She felt tired and depressed, and the cold continued. She would sniff and swallow the secretion. This con-

tinued for nearly 2 months—until deeper insight into the oral demands and aggressions was achieved.

During this period, the patient's dreams were strikingly and predominantly oral. For example, she dreamed that a cannibalistic dog with huge teeth approached her. Another girl vomited and the patient *felt* like doing so. After a metabolism test she dreamed that she was passionate and asked the analyst what to do about it, he gave her a big stick of candy and she chewed it up and swallowed it. No soiling appeared in her dreams at this time. The patient spontaneously reported that nocturnal oral activities occurred in connection with the oral dreams—swallowing, mouth breathing while sleeping on her back and teeth grinding. These activities resulted in a soreness of her throat in the morning which, with the concomitant nasopharyngeal secretion and mild depression, gave the symptoms of a cold. The nasopharyngeal secretion appeared regularly in connection with her thwarted oral demands.

The fourth patient, a single woman in middle life who came to analysis because of a suicidal attempt, had been subject to severe colds in the winter. These colds were of an influenzal type, with anxiety, restlessness and some hypochondriacal fears of tuberculosis. A low-grade fever (rarely over 100° F.) was an almost invariable concomitant. The local upper respiratory symptoms, though present, were not in the foreground. During the analysis these severe colds (including the fever) occurred repeatedly whenever the patient became distressed and panicky because of her intense thwarted receptive demands and consequent oral and anal aggressions. Although the patient violently denied even the possibility of psychogenic factors in her colds, nevertheless, as her strong receptive demands and consequent

rage at thwarting became conscious and she became emotionally relieved, the colds disappeared and have not returned. A year later this patient felt herself on the verge of a cold, but recognized it as an expression of an emotional strain caused by unusual demands upon her as well as by the threatened loss of a mother substitute. The patient was thus able to handle her emotions psychologically without expressing them in organic symptoms.

"A homosexual boy, not subject to colds, developed a strong passive transference which he tried to deny. His dreams were predominantly of an oral aggressive nature — often cannibalistic. One day he suffered a severe thwarting in the transference in the form of a refusal of a request. Next morning he awoke with a cold and sore throat. During the analytic hour he realized his emotional reaction. The cold disappeared by the next day.

"A very narcissistic middle-aged man developed a strong passive dependent transference with frankly oral receptive dreams, as of being given the breast. As this material became clear, he proudly and bitterly denied it and with a superior air of independence refused to avail himself of the opportunity of continuing his analysis during the usual summer vacation. At the end of a week, a condescending letter appeared, and 3 days later another one saying that he had been in bed with a severe cold with low grade fever for 3 days, clearly indicating that he wanted the analyst to urge him to resume the analysis. The sequence, 'receptive thwarting-rage-cold,' is apparent. Upon resuming the analysis after the vacation, he reluctantly admitted the intensity of the passive attachment and his narcissistic rage at having it, and at the thwarting, and then confessed that it was this that so upset him."

The author points out that of course all hostile feelings do not produce colds. But in the cases reported much repressed anger was present at the time the colds occurred because of the receptive thwarting and also from injury of the patient's feelings of self-love. The colds disappeared when the emotional tension due to the thwarting of these demands was relieved by making these demands conscious to the patient.

The fact that "a young woman of 30, of the 'clinging vine' type, with a variety of physical symptoms, denied her strong dependence and receptivity because of her narcissistic resentment of men, her penis envy. She would cling and demand and yet simultaneously freeze and maintain that she was above taking anything from any man. However, she tells of reading 'sexy' stories before retiring at night, with consequent vaginal secretion and occasional vaginism. Attempts at intercourse cause vaginism. When, after 7 months of analysis, the oral and genital receptive wishes toward the analyst became strong and close to consciousness and appeared clearly in her dreams, she developed chronic symptoms of cold in the head, with sniffing, swallowing of postnasal discharge (the secretion was clear, not purulent), mild soreness of the throat, a continual feeling of weepiness, congested conjunctivae. She said she rarely wept, but felt as though she were always 'weeping inwardly.' In addition, there appeared anorexia, constipation, and leukorrhea.

"In the patients observed, the nasal catarrhal secretion appeared regularly, along with the other symptoms described, in periods of intensified unsatisfied receptive demands. It appeared only at these periods, and disappeared when the analysis made the emotions more fully conscious. In 15 cases it greatly decreased in frequency of occurrence fol-

lowing psychoanalysis. There is, therefore, no doubt that it can be caused by emotion. What remains incompletely solved is the causal sequence between specific emotions and the catarrhal secretion "

The author feels from clinical evidence that the nasal catarrhal secretion can be stimulated by strong intaking tendencies expressed in the oral and upper respiratory region instead of, or as well as, in the genital. This fits in with similarity of the lining mucosa and presence of erectile tissue in both the genital and nasal regions. There are also clues to the connection of the catarrhal secretion with eliminating impulses "At the times when these colds appeared, the patient showed concomitant symptoms in other regions. They all showed some diarrhea or constipation, and the third patient had a transitory urinary urgency which appeared following a dream of urinating on the floor of the analyst's office "

"In considering psychogenic organic disturbances, the degree to which one organ is disturbed more than another is probably always a matter of quantity and emphasis. The reasons for the choice of organ, why one organ may be involved so much more than another, have not yet been elucidated. To say 'constitutional' begs the question. The choice probably depends largely upon past experiences of all kinds and also upon the nature of the predominant emotions.

"During periods of emotional disturbance, the patients showed emotional connections not only with the colds they developed but also with other physical activities and symptoms. These other symptoms were of a kind which frequently accompany the 'common cold' "

"The general feelings of fatigue, loss of energy, malaise, etc., were seen in the analyses of these cases to be chiefly manifestations of mild depression. How-

ever, this is only one factor. In other cases these symptoms may be entirely on a toxic or other basis.

"Along with the other symptoms, 3 of the female patients developed leukorrhea and the condition was diagnosed by the gynecologists as catarrhal vaginitis. This is of considerable interest in connection with the catarrhal nasopharyngitis, and suggests that the emotional stimuli are essentially the same for both.

"It might be expected that an individual's local and general resistance to colds would be decreased by the local irritation and general depression which result from emotional causes, and that he would therefore be more susceptible to infectious colds from contagion or from the viruses in his own throat. This may frequently be true, but it does not seem to be the main mechanism in the cases reported in this paper. For in these the onset was often sudden; the duration varied from minutes to months, without purulence or other conclusive signs of secondary infection, and when a burst of insight into the emotional situation occurred, the symptoms disappeared rapidly.

"Colds of this type are apparently much more related to allergy (in this case hay fever) than to infection. The interrelationships are, of course, far from simple. But whatever the interrelationships of virus, changes in temperature, other agents, and allergy, it seems certain that the colds described in this paper belong to that group of common colds in which the allergic reaction and not the infectious is in the foreground, and that, in the cases herein reported, the unconscious emotional situation was the main etiological factor. When more is learned of the physical and unconscious emotional factors in hay fever and in other allergic conditions further light

will be thrown upon the specific emotions and upon the entire problem of this group of colds.

"The striking improvement, but incomplete immunity, which resulted after psychoanalysis may be accounted for in 2 ways. The first is that the neurotic mechanisms involved were not entirely overcome (and we know that traces always remain). The second is that the patient has been cured of neurotic colds, and that the occasional ones he now gets are due to other causes

"The physical treatment usually employed for colds probably has much more of a psychological effect than has been realized. The importance of the oral receptivity may be recognized in the old maxim 'Feed a cold—starve a fever.'"

The author concludes that "in the patients reported, colds occurred regularly in situations of frustration of strong, mostly unconscious, receptive demands with more or less repressed rage. In the opinion of the author, the evidence in these cases shows that the relationship is causal. This observation in no way implies that all emotional states of receptive thwarting result in colds, nor obviously that this etiology is in any

sense exclusive. The emotional factor is only one of several (infectious agents, irritants, allergins, temperature changes, etc.), operating separately or in combination, and may be of greater or lesser importance or prominence in any individual case. Nor are the emotions and mechanisms here described necessarily the only ones which can produce the picture of the cold. In the cases reported in which the emotional factors played a prominent rôle, the symptoms seemed more closely related to allergic than to infectious conditions, although nothing positive can be concluded on this point.

"The emotional impulses stimulate physiological activities in other regions of the body. These result in the other symptoms which frequently accompany colds: gastrointestinal disturbances (anorexia, nausea, diarrhea, colitis, constipation), headache, and, in women, leukorrhoea. The fatigue, malaise, etc., are often, at least in part, manifestations of mild depression. Fever, apparently truly psychogenic, occurred in 2 cases. The whole condition is utilized in the services of masochism, passive indulgence, secondary elaboration and various other secondary gains."

PSYCHONEUROSES

By LOUIS H. TWYEFFORT, M.D.

Introductory—Within recent years, the rôle of emotional factors as contributory toward, and in some cases causative of, physical disease has been increasingly emphasized. Until 4 years ago, this considerable but scattered literature had never been gathered together, correlated or evaluated. This has very ably been done by H. F. Dunbar³¹ in a monograph which is a survey of the literature on psychosomatic ("mind-

body") interrelationships as it has appeared between 1910 and 1933, and covers in its bibliography over 2200 titles.

Since the dawn of medical knowledge it has been known that emotional factors will alter physiological processes, but it has only been within recent years that medicine, especially through advances made along psychiatric investigations, has become aware of the intimate

correlation between emotions and bodily changes. Recent research, chiefly along the lines of psychoanalytic approach, has revealed considerable thought-provoking data in connection with some of the so-called "constitutional diseases," especially essential hypertension, hyperthyroidism, hyperglycemia, asthma, various skin diseases, and certain functional gastrointestinal disorders: peptic ulcer, "mucous colitis," and "spastic colitis." That emotional factors will disturb physiological processes has always been recognized, but evidence is accumulating which suggests that long-sustained emotional states can bring about irreversible physiological changes, namely, actual structural alteration, tissue pathology (organic disease).

Theories — The various theories evolved to account for this psychosomatic ("mind-body") interplay are reviewed by Leo Stone¹² in an article which postulates the "possible role of psychic disorder as a major etiological agent" in morbidity. In this connection "the rigid distinction between psyche (mind) and soma (body), between organic and psychogenic disease," should gradually be abolished. That emotional states will bring about profound alterations in the bodily economy has been proven by Cannon's classical experiments in physiology. For instance, coexistent with rage, profound involuntary and mostly unconscious changes occur in the blood chemistry (especially sugar), in the endocrine activity (*e.g.*, adrenals) and in the balance of the autonomic nervous system (changes in respiration, heart rate and in gastrointestinal motility). The chief central origin of these visceral and humoral reactions is in the midbrain (hypothalamus), referred to by Cannon as the "Emotional Level."

Any practical, general hypothesis which would attempt to explain the rôle of the

emotions in disturbed physiological processes, must first set forth in simple terminology the meanings of several important terms, "psychical energy," "instincts," "emotions" and "the unconscious." In the realm of physics, many of its problems are explainable in terms of "energy" even though we are quite ignorant as to the ultimate nature of this energy. It is just as logical in any attempt at understanding mental processes to postulate the existence of "psychical energy" as the driving force behind mental functions. (That physical and psychical energy are probably but manifestations of a single driving force as yet unknowable, is in line with present-day theories which emphasize a monistic approach to causation as against the dualistic approach [mind *versus* body] of a generation ago.) More specifically, this "psychical energy" is at times termed "libido." Being a source of constant potential power, this energy seeks expression in the form of "instincts" (man's primitive urges, drives and strivings). The term "emotions" refers to the subjective aspect of this instinctual activity in a complex organism. And finally, the repository of the individual's primitive urges ("instincts") and of his past experience is held to be that portion of the mind referred to as the "unconscious." Outstanding among the instinctual drives are those of aggression, fear, love, hate, sex and hunger, each of which may be conceived of as being charged with their own specific energies constantly seeking for expression. Since the law of the conservation of energy holds just as rigidly in the mental realm as it does in the realm of physics, total suppression or annihilation of psychic energy is just as impossible as is that of physical energy. The acceptance of this concept is important in understanding the following exposition

In his schematization of mental activity, Stone uses the term an "emotional event" to express any specific mental activity. The source of the instinctual energies (the libido) may be thought of as having its physiological representation in the hypothalamus (= Cannon's "Emotional Level"), a region which experimentation has proved to be intimately connected with the emotional life. (This level, in Freudian terminology, is representative of the "Id" portion of the adult personality, the mainspring of the adult Unconscious.) According to the statements made in the preceding paragraph, and because of its specific charge in terms of energy, an "emotional event" must seek expression. From its site of origin, the hypothalamus, an "emotional event" may radiate over 1 of 2 varieties of pathways either it may travel over the thalamocortical fibers to the cerebral cortex and there appear in consciousness (causing subjective "emotion") and expressing itself in action over the (voluntary) corticospinal nervous system (which innervates "voluntary" striated muscle fibers), *or else* it will travel over the (involuntary) autonomic nervous system (which innervates "involuntary," smooth muscle fibers and the endocrine glands). However, the (voluntary) corticospinal nervous system does not respond automatically. It is governed by the Will (equivalent to the Freudian "Ego" portion of the adult personality), in itself a function of the cerebral cortex, especially of the frontal and prefrontal area. Because of the social unacceptability of the indiscriminate free expression of these instinctual drives, the Ego, assisted by the unconsciously acting force of Repression, serves as a moderator of the instinctual drives, frequently completely inhibiting their overt expression. When instinctual drives are per-

sistently blocked, "the terrific upset of the internal milieu, over which the complex organism has no voluntary control, goes on without physiologic outlet, and evanescent disease arises." As well-known examples of the persistence, sometimes the exaggeration, of involuntary emotional activity which occurs when the lower centers are freed from the controls of the higher neural levels, Stone mentions the thalamic syndrome; clinical dissociations between volitional and emotional facial innervation; the exaggerated laughter and crying of pseudobulbar palsy as well as of nitrous oxide anesthesia; and the actions of decorticated experimental animals. He further comments: "It is hardly likely that suppression of emotional energy by an intact cortex actually decreases its quantity." It is probable that in the presence of inhibition, "the cortex, when intact, either absorbs and utilizes part of the energy, directly or indirectly" in the formation of mental symptoms (fears, anxiety, compulsive thoughts, phobias, amnesias, etc.) or in normal thought processes leading to sublimation, or "diverts a greater portion of (this energy) into visceral or humoral (*i.e.*, endocrine) channels than is necessary when cortical inhibition is removed." The conclusion would be that "blocking of powerful instinctual impulses can cause profound physiological disturbance." Thus if the manifold strivings and complexes of the adult "unconscious" mind are "cut off entirely even from indirect cortical conveyance (*i.e.*, sublimation), they must be turned with heightened intensity and hopeless chronicity on the viscera and bodily fluids."

A stepping stone to an understanding of psychosomatic interrelationships is offered by a consideration of one of the psychoneuroses, conversion hysteria. In this disturbance, anatomical changes are

rare or at the most mild. Slight vasomotor changes may occur, but they are easily reversible. Ankyloses when they develop are looked upon as secondary changes. As actually proven by analytical investigation, the hysterical symptom has a definitely demonstrable symbolic significance. In hysteria we may "conceive of the entire pathological tension as occurring on a cortical level, or near it, barely excluded from admission into consciousness, and thus barely excluded from possible stimulation of the corticospinal (*i. e.*, voluntary) nervous system. . . . In place of either complete repression or full expression . . . a literal compromise is struck in a directly or symbolically involved portion of the body, in a distortion of the will (*e. g.*, hysterical paralysis) or of perception (*e. g.*, hysterical pain or anesthesia)." In the cases where the conversion symptom is objectified in the form of vasomotor changes, this "may be due to cortical-hypothalamic connections, or to autonomic representation in the cerebral cortex itself."

According to Stone, the availability of cortical expression to a primitive impulse (*i. e.*, its expressibility in motor behavior, speech or thought) "varies inversely with the degree of frank instinctual admixture in a given impulse . . . because of the anticipated external risk" (of social disapproval, of being intolerable to the Ego, etc.). Similarly, "the less adaptable is the primitive impulse to centrifugal expression of any type (*i. e.*, to expression over the voluntary nervous system), the more completely is its neural energy confined to the endocrine and vegetative nervous systems."

In the presence of more profound and long-standing deep emotional states involving intense repression of instinctual drives, "the instinctual levels presumably discharge through entire neural and

endocrine systems, with a relative absence of symbolic localization (as compared with conversion hysteria), and it is in them that we may assume the materializations or Anlagen of profound organic disease." Among such chronic disturbances which may be engendered are those of tissue growth, of sugar metabolism, of vascular tension, of cardiac rate and rhythm, etc. Stone furthermore stresses the point that organic disease and psychosis (as against psychoneurosis) "both represent alternative experiences of profound instinctual and vegetative disorder." By contrast, visceral or conversion symptoms (as found in conversion hysteria) and psychoneurosis represent relatively superficial disturbances. "In the psychosis, through a process analogous to summation of stimuli, thalamocortical blocks (*i. e.*, repression) are overcome, and the voluntary (Ego) nervous system becomes, to varying degrees, the direct instrument of the instinctual levels. . . . Thus the viscera are spared the full impact of the pathologic autonomic activity." The determinants governing the selection between the psychotic or organic methods of expression for intense emotional conflicts are as yet not definitely known, but may depend upon gradual accumulation of instinctual tension as against the sudden overwhelming by specific stimuli from the environment.

Some substantiation of the above viewpoint is offered by the frequency with which prodromal physical symptoms precede the frank onset of a severe psychosis. Stone would regard these symptoms as constituting "threats against life" in the form of potential later severe physical illness "which are averted only by the eruption of manifest psychosis, whereafter (the somatic symptoms) often disappear." Such a trend of events is frequently noted especially in schizo-

phrenia, whose early hypochondriacal phase is a matter of common observation. Similarly one frequently sees cases in which a severe long-standing organic complaint (such as a mysterious precordial pain) becomes displaced by a psychosis. (Some might interpret this sequence of events in terms of the organic disease having later caused the psychosis.) But the reverse is frequently likewise noted, dramatic improvement in a psychotic individual developing severe organic pathology (*e. g.*, coronary occlusion, etc.). The psychoanalytical interpretation of such a sequence of events inclines to view such a physical catastrophe as having satisfied the "need for punishment" which had been engendered by the existence of the unconscious aggression.

The keynote to the psychogenesis of certain forms of organic disease is thus to be found in the "forced internalization" of certain instinctual tendencies, especially strong erotic and strong aggressive tendencies, which results in morbid organ tensions. Erotic impulses, as against deeply destructive impulses, are more liable to attain to some type of cortical conveyance because "they are at least susceptible to sublimation or relatively benign conversion and are less liable to be forced into persistent and exclusive autonomic channels." Thus the emotional as well as the physical health of the individual is closely connected up with externalization of instinctual energy. Action, while promoting the greatest relief of such tension, carries with it at the same time the greatest external threat (*i. e.*, risk of disapproval). Whereas speech occupies, as it were, a midposition, thought, on the other hand, offers the least relief but coincidentally carries with it the least grave external threat. Thus the symbols and phantasies of the thought life "represent

a constant effort to translate the physiologic energies of instinct into a form adequate for corticospinal expression (in a somewhat disguised form), or at least into the dissipation of pure thought."

In his conclusion, the author states that whereas medicine has been coping with "exogenous diseases" with increasing success, the death rate from "degenerative diseases" increases steadily and "their etiologic mystery diminishes only imperceptibly." On the basis of the central origins of the autonomic nervous system and its important relationships on the one hand with the emotional life, and on the other hand with alterations of visceral function, the hypothesis is advanced that neurotics and sufferers from unmistakable severe organic diseases "may at times be suffering the late effects of deeply buried and chronic instinctual conflict." From such a standpoint, many "endogenous diseases," at least the "diseases of unknown origin," offer challenging problems. Under such a heading can be listed such clinical pictures as essential hypertension; exophthalmic goiter; peptic ulcer; bronchial asthma; atherosclerosis and its derivative diseases; diabetes mellitus, neoplasms, etc. In early constitutional disease and in early endocrine dysfunction "it is possible that the organs which perhaps determine the original character of the instincts or libido more than any others, are conversely vulnerable to instinctual distortions due to early experience, and that profound alterations in physique and body chemistry (including immunity) may be deeply psychogenic." Whether these profound psychophysiological disorders are within the scope of psychotherapy after anatomic change has occurred is still open to question. Nevertheless, there appears to be considerable evidence accumulating to the effect that emotional conflicts lead to profound

neural imbalances in such a way that a psychogenic concept of at least certain organic diseases is a challenging hypothesis.

Physiological Mechanisms of Emotionally Conditioned Anatomical Changes

L. Alkan³³ (after Dunbar), has brought forward the most comprehensive simplified hypothetical schematization as to how anatomical changes may occur as the result of emotionally conditioned stimuli. Briefly, the way in which the end-organ reacts to psychic influences depends upon its anatomical structure, that is, upon the nature of its elements under the influence of the vegetative nervous system.

These elements are of 2 chief varieties. (a) *Contractile elements* (chiefly smooth musculature governing tonus) and (b) *secretory elements* (glands of internal secretion of external secretion). With regard to the *contractile* elements, emotionally conditioned motor disturbances may lead to anatomical alterations in several ways. (a) Lasting contraction (especially spasm) in hollow organs may, because of compression, produce an anemia of the region involved, resulting in a combination of mechanical injury and lack of nutrition. Thus there may follow regressive and necrotic alterations of the tissues of the region, or such pre-existing changes may be aggravated or reactivated (*e.g.*, peptic ulcer, latent idiopathic ulcerative colitis). (b) Lasting or sufficiently often repeated spasm of tubular organs (or their paralysis, *i.e.*, total loss of tone) may bring about (1) Muscular hypertrophy of proximal parts, and secondarily their dilatation (*e.g.*, idiopathic dilatation of esophagus; hypertrophy of left ventricle in essential hypertension), (2) stasis and pathological changes through alteration

of concentration or fermentation changes in fluids which normally circulate freely (*e.g.*, solitary cholesterol stone in gall bladder; congestive esophagitis). (c) If there is a source of infectious material above a long-lasting circular spasm, the infected fluid is dammed up under increasing pressure making for a febrile, purulent inflammation which may lead to perforation, thrombosis, etc. (*e.g.*, infection in gall bladder obstruction).

With reference to the *secretory* elements, increased or decreased psychically conditioned secretion may lead to far-reaching primary and secondary anatomical disturbances in the endocrine organs (*e.g.*, psychically conditioned diabetes or Graves' disease). Similarly, quantitative or qualitative changes in external secretions may have various anatomical results (*e.g.*, peptic ulcer, bronchial asthma, etc.).

In his paper, Paul Schilder³⁴ prefaces his remarks with the thought that in a "functional" case there may be some organic change not found by our methods of examination, or that the "so-called organic case is perhaps not so independent of psychological processes as it may seem in the beginning. We are not entitled to say that the organic case should not be treated from a psychological point of view." He further elaborates the theme that psychological problems may use organic symptoms to manifest themselves, and approaches the basic symptoms of disease in terms of their psychological "meanings," as though the organism were speaking in a sort of symptom language.

For a correct understanding of these implications one must understand the patient in terms of his life situation, and as a result of his early life experiences. "Human problems of specific type have specific relations to the specific organ systems" involved in the symptomatol-

ogy. Accordingly, one should try to fathom the general psychological meaning of the symptoms in any specific case. Following a discussion of the psycho-analytical implications of the basic symptoms of disease, those having to do with the surface of the body, with its openings, with the senses, and with the inside of the body, Schilder comments upon the more general symptoms.

"Anxiety" occurs always in the form of a danger signal and sums up the dangers which may attack the outside of the body, its openings or its interior. It is often connected with the fear of social disapproval when the danger lurks in the sexual drives, at other times with the fear of death.

"Dizziness" when on a psychogenic basis is viewed as "the psychological sign of sensual and moral disorientation to the world" and is intimately connected with conflict arising from the instinctual drives, or when the integrity of the individual is threatened as in the beginning of disease.

"Nausea" emotionally induced represents "the beginning of an attitude of rejection," while "weakness" means giving up or being forced to give up, and may be a sign of the individual being unable to handle his own problems and coincidentally assuming a submissive attitude. Occasionally it may indicate a feeling of being unable to act because of unconscious or conscious feelings of guilt.

"Fatigue" in its psychological implications is closely allied to weakness. In functional cases it may be a sign that the individual does not feel equal to his tasks any more. It may occur when the unconscious aggressive tendencies become too threatening.

In interpreting the psychological meanings of symptoms it is most important also to have clearly in mind a concept

of the individual's aims and life goal. The aim of psychotherapy should be to give the individual a deeper understanding of his goals and instincts. It thus resolves itself into "a process of truth finding" in which one aims to re-enact the basic psychological problems and the historical development of the symptoms.

Specific Organ Involvements

The Skin—In a consideration of "The Emotional Factor in Skin Diseases," E. T. Bernstein^{35, 36} states that "there is a definite field where dermatology and neuropsychiatry meet and where co-operation between these specialties can be mutually profitable and instructive." He maintains that "the psyche, through the mediation of the sympathetic nervous system acting on the smooth muscle of blood vessels, produces certain common phenomena in the skin, such as blushing, pallor, sweating, etc. . . . Few deny their relation to emotional states. When, however, chronic alterations of an irreversible nature are produced in the skin, there is a tendency to deny the primary importance of the psychogenic element." This author is nevertheless inclined to feel that truly psychogenic skin lesions do occur, the emotional elements influencing the blood vessels by way of the sympathetic nervous system "causing either vascular dilatation with its associated exudative processes, or vascular constriction with its subsequent tissue defects." Several case histories are given in which the psychic factor appears highly important. In 1 case severe urticarial lesions appeared for the first time in a patient of 22 after she had eaten some sea food. Subsequently the mere sight of sea food was sufficient to precipitate a similar attack. The author also lists other dermatoses which in certain cases appear to be psychogenically conditioned, such as

herpes hystericus, various types of skin gangrene, "hemorrhages into the skin, various types of edema, eczematous eruptions, changes in the hair resulting in acute depigmentation, alterations in the nails, and peculiar disturbances in sweat secretion." Certain types of pruritus often possess an emotional component, which may even be primary. The rapid cure of warts by suggestion where long-standing routine dermatological procedures have failed, is also referred to, with illustrative case material.

The functional element in some 20 cases of "angioneurosis" manifesting various types of arteriospasm is reported upon by P. L. Goitem.³⁷ These cases were investigated by psychoanalytical methods. The author makes the comment that "disorders of this kind take on a new significance when understood from the psychological angle, and when it is realized that not only vascular, but sympathetic, endocrine, thalamic and psychic levels are all playing a part."

Allergy; Asthma and Hay Fever

H. F. Dunbar,³⁸ in some observations, reviews the recent literature on this subject (some 200 articles which have appeared during the last 4 years) and states her own findings in 3 cases which she has analyzed. Some of the more important findings in the literature are here given:

1. The symptoms of both asthma and hay fever may be brought about, or eliminated, by hypnosis and suggestion.

2. Specific attacks may be precipitated by specific traumatic psychic experiences or stimuli.

3. When the symptoms have been eliminated psychotherapeutically, skin reactions to specific allergens may remain.

4. There are times when even sensitive patients can stand the allergens without their producing symptoms.

5. Psychic factors play a rôle in the skin tests themselves.

6. Allergic reactions most often are encountered in the "leptosomic" bodily build.

7. Hypersensitivity is a variable factor changing with geographical conditions, periods in life, endocrine and metabolic changes.

8. Some physicians appear completely unwilling to recognize any psychic factors in allergy. Some consider at least asthma as a neurosis.

9. "Although specific events in the emotional life may precipitate specific attacks or determine localization of allergic skin reactions, the real etiology lies in the total personality structure, psychologically and physiologically considered."

10. Any shock and mere exposure to the allergen is not an adequate stimulus.

11. In these cases there may be alternation between symptomatology organically expressed and the appearance of psychological symptoms.

12. From a personality point of view, asthma and hay fever patients are ambitious, hyperactive, self-absorbed and mentally sensitive.

13. Schizophrenic patients are immune to the influence of pollen.

Some of Dunbar's findings in her own patients, stated in Freudian terminology, revealed a marked predominance of anal and oral sadistic material, involving sexualization of the respiratory function and great interest in the sense of smell, marked unconscious aggressive tendencies in the patients showing asthma, and an apparent "compulsive" character; marked ambivalence, hostility which seemed constantly on the point of going into action, with the result that the individuals were in constant terror; a weak Ego organization and an inadequately assimilated Superego, somatic symptomatology which appeared to be of an incapacitating and punitive nature, though, in an indirect way, simultaneously also satisfying the aggressive impulse, and libidinalization of certain organs and functions. In her 3 cases which were analyzed intensively, the organic symptoms cleared up with the treatment of the psychic pathology. She considers the psychosomatic problem as

"the most vital problem confronting medicine today."

C. H. Rogerson³⁹ presents detailed psychological studies on a group of 30 children presenting the symptom-complex of asthma-prurigo. He stresses the frequent occurrence of special personality features and special environmental difficulties which are closely related to the attacks. Among the personality traits constantly encountered were those of aggression, domination, overanxiety, tenseness and insecurity, whereas the environmental setting was frequently characterized by overprotection and thwarting by oversolicitous and anxious parents; tension in the home, frequently because of quarrels between the parents, jealousy toward siblings; or the patient being cast in the rôle of an only child.

Heart—The "Psychologic Factor in Cardiac Pain" is discussed by E. Wittkower⁴⁰ in a study of a series of patients from the point of view of: (a) Personality structure (before the onset of the complaint); (b) the specificity of the emotional factor in the formation of cardiac pain, and (c) a theory for the dynamics of this variety of pain. Since an event which in one person will provoke a severe emotional reaction may leave another hardly affected, it is imperative that the nature of the specific suspected traumatic event be studied against the background of the total personality.

W. C. Menninger⁴¹ stresses the importance of "unconscious" emotional factors behind many functional cardiovascular disorders, and illustrates the mechanism of these unconscious factors. Reviewing the literature, he states that from 20 to 50 per cent of individuals consulting general practitioners or cardiologists for cardiac disorders have no demonstrable organic lesion. He is inclined to score the too common tendency

of speaking in terms of a hypersensitive autonomic nervous system or an autonomic imbalance, and feels that in most instances the fault lies in a psychogenic stimulus which is excessive or unduly protracted. He reminds us that "extra-systoles may be produced by psychic stimuli, and paroxysmal tachycardia is frequently recognized as psychological in origin." Even in actual organic heart disease psychological factors may be just as effective etiologically: "The emotional disturbance gives rise to a functional heart disorder; the emotional disturbance continues over a protracted period and the functional disturbance in the heart gives rise to structural changes." Even in heart lesions on an infectious or toxic basis, the psychological influences may be of importance. Menninger states that through the findings of psychoanalytical studies, there is increasing evidence that the emotional content of "repressed" ideas, especially when connected with the emotions of hostility, hate, aggression or jealousy, play an important rôle in the causation of certain functional cardiac disorders. The psychotherapeutic handling of the milder grades of these disturbances is presented in a manner applicable by the general practitioner.

Essential Hypertension—F. Alexander⁴² prefaces his consideration of "Emotional Factors in Essential Hypertension" with the statement that it is common knowledge that specific emotional situations are connected with specific physiological changes. For example, embarrassment is followed by blushing, despair by sighing, sorrow by weeping, amusement by laughing, fear by palpitation, pallor, interruption of respiration, etc. A comprehensive analysis of bodily reactions to specific emotions is still lacking, although Cannon has correlated some significant findings in connection

with blood pressure rises in rage and fear. Alexander's systematic studies of hypertensive patients during psychoanalysis indicate that the mobilization (*i e*, bringing into consciousness from their unconscious source) of repressed aggressive tendencies is associated with significant fluctuations in blood pressure. A number of these patients have been relieved of their hypertension. He would be inclined to formulate a tentative hypothesis according to which the chronic effect of repressed hostile tendencies is one possible factor in contributing to the hyperpyrexia. Not only the chronic stimulus of unconscious (repressed) aggression may cause the above picture, but also the chronic stimulus of fear.

Hyperthyroidism—In their studies on "Hyperthyroidism and Personality," based on a series of 15 cases, W. T. Brown and E. F. Gildea⁴³ stress the frequency of emotional shock or strain just prior to the recognized onset of the illness. Their investigation was intended as an answer to the question as to whether "there is any sort of susceptibility or readiness (in these individuals) biologically to react and experientially to express themselves in this manner?" Thirteen of the cases showed evidence of a strong familial tendency toward nervous instability. All the cases showed personality traits characterized by an extreme feeling of personal insecurity with a strong sense of responsibility and a tendency to suffer in silence. Frequently they attach themselves to someone (parent or surrogate) for guidance and protection. The majority, long before the development of hyperthyroidism, showed signs of endocrine and autonomic nervous system imbalance. In most cases, the gross symptoms of hyperthyroidism had been present more than a year before they sought medical help, and frequently they persisted in attempting to

fulfill their responsibilities in face of taxing manifestations. In all cases a definite disturbing situation had preceded the recognized onset of their hyperthyroidism, and the nature of the situation was usually in the form of a threat to the individual's security, either by loss of guidance and protection (frequently of a parent), or increased responsibility. Of the 13 cases which were operated upon, 12 revealed hyperplasia of the thyroid, 1 an adenoma. Significantly these investigators remark "With whatever success treatment is directed toward the thyroid gland, the fundamental way of experiencing of the patient is *not* altered. If, after treatment, the patient returns to the same or a new stressful situation or experiences further shock, recurrence of the whole picture of hyperthyroidism is likely. Relief from stress and strain is essential to continued recovery." They conclude that these patients present 4 points in common: (a) A constitutional predisposition, (b) a way of experiencing which involves a peculiar susceptibility to emotional shock or strain, (c) a severe disturbance in the form of a sudden shock or a prolonged strain prior to recognized onset, and (d) hyperplasia of the thyroid. They also feel that hyperplasia of the thyroid is a secondary occurrence dependent upon the autonomic imbalance, and a certain innate sensitiveness of the gland. The importance of dealing with these patients in terms of their total personality, instead of relying too implicitly upon the surgical scalpel, is stressed.

Gastrointestinal Tract—Peptic Ulcer—D. T. Davies and A. T. M. Wilson⁴⁴ examined a series of 205 patients with peptic ulcer comparing them, as a control, with 100 patients with hernia (a "mechanical" disorder unrelated to emotional disturbance). In 84 per cent of the ulcer patients, the symptoms began

soon after the occurrence of some event affecting the patient's work or finances, or the health of his family. Only 22 per cent of the hernia cases gave such a correlation. Of 52 relapses in the ulcer cases, 42 coincided with some event causing anxiety to the patient. A significant excess of the ulcer patients showed undue tension long antedating their ulcer symptoms. As a group, the ulcer patients showed a definite tendency toward a predominant facies and body type, and a personality characterized by excessive drive and intense mental and physical activity. The traumatic events must, they feel, "be implanted in a special soil." Their conclusions are to the effect that chronic peptic ulcer "is an example of the influence of the mind in producing structural change, and that successful therapy depends upon the attention being given to the whole individual."

Nonspecific (Idiopathic) Ulcerative Colitis; Mucous Colitis—From a psychological (nonanalytical) study of 9 cases of nonspecific ulcerative colitis, W. T. Brown, P. W. Preu and A. J. Sullivan⁴⁵ conclude that in a certain type of personality ulcerative colitis may be precipitated by an emotional disturbance. Character traits displayed were those of egocentricity, passivity, insecurity, emotional tenseness and immaturity, and a failure of emancipation from parents or their substitutes. All the cases showed a "way of experiencing characterized by a tendency to give up in the face of difficulty." A uniform finding was the presence of low energy endowment, emotional lability, ready inclination toward anxiety or apprehensiveness. In a group of 30 cases, there was not a single successful marriage nor an instance of complete emancipation from parental ties. Emotional instability or personality defects were frequently encountered in

parents and siblings. In 8 of the 9 cases, an emotionally disturbing life experience occurred just before or at the time of onset, in the nature of marital discord, sexual fears, or feelings of guilt.

Wise advice considering the general management of functional disorders of the gastrointestinal tract is given by W. C. Menninger⁴⁶: "That such disorders are primarily emotional in their causation is a fact granted by nearly everyone. The point is stressed, however, that such individuals should have the benefit of an accurate, penetrating, and detailed analysis of the psychological component of their illness, and that only as we understand the dynamic aspect of the personality disorder can we adequately treat the individual. Treatment in all cases must be directed toward the total personality and not toward the stomach or the intestines or the colon alone."

Psychoanalytical Interpretations of Gastrointestinal Disorders (Especially Peptic Ulcer; Mucous Colitis; Constipation)—As surmised by F. Alexander⁴⁷ in his text "The Medical Value of Psychoanalysis," the emotional problems acting as etiological factors in gastrointestinal disturbances are probably of a specific nature. The actual life situation (*i.e.*, traumatic event) acts only as a *precipitating* influence. The true *causative* psychological factors originate in the development of the individual's personality, and only knowledge of that development (as gained through analytic investigation) can explain the later reactions to acute traumatic situations.

Inasmuch as the functions of the intestinal tract are threefold (intake, retaining and elimination), it stands ready as an organ through which emotional trends and tendencies may express themselves, such as the *wish* to receive (or take), the *wish* to retain, or the *wish*

to give (or eliminate)—when the expression of these trends through the (voluntary motor) central nervous system is inhibited because of inner conflicts. Depending upon the nature of the emotional trend seeking expression, the reaction may be of the gastric type, of the colitis type or of the constipation type.

Gastric Type of Reaction—(Associated symptoms: Epigastric distress, nausea; heartburn; belching). The personalities exhibiting this type of reaction show intense oral-receptive tendencies (= a craving for affection). The "wish" seeking expression is that of wanting "to be taken care of, to be loved," expressive of receptive tendencies, of a need for help, of an underlying wish for dependence. Because these tendencies are incompatible with their Ego's desire for independence and activity, they are suppressed, making for conflict. Consciously, these individuals appear self-sufficient, make a real effort to assume responsibilities, like to be leaders, appear full of drive and initiative. Nevertheless, the symptoms betray the underlying conflict engendered by the thwarted receptive wishes. The psychological conditioning of the disturbed physiology is explained as follows. The child experiences the first gratifications of its receptive tendencies in being nourished. This early results in an emotional association between the passive wish to be loved, to be taken care of, and the physiological functions of nutrition. If the wish to be loved (taken care of) is suppressed, then it mobilizes the emotionally associated wish to be fed, and this wish to be fed *in turn* may then serve as a specific and chronic stimulus influencing the stomach (*i. e.*, its physiological functions). When this occurs, one may think of the stomach as speaking a sort of "physiological language" and

expressing a "hunger" for receiving love and help. Such a patient may then be thought of as wanting food not because of organic hunger, but as a "symbol" of love and help. The result of this constant wish, seeking expression, is chronic hypermotility and hypersecretion.

Colitis Type of Reaction—(Associated symptoms: diarrhea, painful cramps). The same conflict, as in the gastric type, exists, but a different solution is attempted, fear and a sense of inferiority being eliminated. Oral-receptive, coupled with acquisitive-aggressive tendencies are said to exist. But the receptive-aggressive tendencies engender a subconscious sense of guilt, giving rise to a wish to make restitution as a reaction formation. The symptom diarrhea is said to have a double "symbolic" meaning, representing the desire to make restitution for what they wish to take from others, and representing aggressive (= eliminative), in contrast to the passive (= intaking), tendencies. (Evacuation, in analytical interpretations, is equated with the infantile expression of attack or aggression.) Consciously these individuals emphasize that they don't receive what they should, in spite of their own (alleged) great willingness to help and give. In this they seem to do only lip service. Before their illness they are often efficient and active, but after its onset, they easily accept a dependent position. (This is in decided contrast to the gastric [ulcer] type of reaction to illness.)

Constipation Type of Reaction—(Associated symptom: constipation). The observable personality seems characterized by a pessimistic attitude toward others, an attitude of not seeming to expect anything from anybody, a belief of not being loved. As against these feelings, there exists an "unconscious" extreme sense of obligation to give. The constipation is thus viewed as "sym-

bolic" of the attitude of spite and obstinancy, of the desire to withhold, and as a reaction against the obligation to give. More specifically, because of feeling that the environment is hostile, the individual also presents an aggressive-revengeful attitude. There results the "wish" to soil with excrements (as does the child), this in turn evokes a fear of retaliation and guilt, which makes for a repression of the above tendencies, and produces chronic constipation (= inhibition of the "wish" to soil).

Diabetes—There is a tendency in the psychosomatic literature to view certain instances of diabetes as the expression of overt or concealed chronic anxiety manifesting itself through continued disturbance of sugar metabolism. (Cannon's work conclusively proved that emotional stress can cause fluctuations in the blood sugar.) It is felt by some writers that, in certain cases, the diabetic picture may be the expression of a neurosis. Whether in such cases the diabetes is amenable to psychotherapy remains to be determined.

Analyzing the emotional factors which frequently come into play, H. F. Dunbar⁴⁸ remarks upon the frequent pattern of life seen in such patients: a steady grind of fatigue and deprivation with an increase in the passive personality tendencies and much resentment. They also are inclined to keep their troubles to themselves and seem unable to share them.

Arthritis—W. Bauer, S. Cobb, and I. Whiting⁴⁹ carried out some interesting studies on 50 cases from the viewpoints of the medical, psychiatric and social services. Although the psychiatric studies were very superficial (slightly over an hour with each patient), 33 of the cases showed "an obvious coincidence of social pathology and the attack of arthritis," 7 a possible coincidence,

10 no coincidence. These investigators feel that these findings emphasize what has long been known to clinicians that "sufferers from rheumatism must be protected from overworry," and they stress the importance of the internist studying "the psychobiology of each sufferer from rheumatoid arthritis, in order that the psychological factor may be evaluated and treated."

General Considerations—At the beginning of the twentieth century there prevailed a preponderant leaning in the direction of organic explanations to explain the nature of pathological changes within the organism. Much progress was made, but the "constitutional diseases" remained almost as puzzling as ever, witness the many hypotheses and the still more numerous attempted therapies which were advanced in an effort to effect cure. It has only been in recent years that a more adequate emphasis has been placed upon the vital etiological rôle which is played by the emotions, as contributory, precipitating and perpetuating factors in these conditions. Some of the major contributions to this specific problem have come from investigators using the psychoanalytical method of approach. This problem of psychosomatic interrelationships, like all developing sciences, is still passing through the stage during which data are being collected, correlated and evaluated. Most of the contributions in the literature center around the emotional settings preceding the onset of the disorders. The second stage, that of the more general therapeutic application of this knowledge, is still to come. Only an occasional report mentions actual therapeutic usage of these discoveries, and in some cases already with success. As pointed out by I. Hendrick,⁵⁰ during the analyses of psychoneuroses there have been incidental observations of definite therapeutic

effects on incidental organic processes. All degrees of chronic and intermittent constipation, minor gastrointestinal ailments, disorders of menstruation, various skin disorders (especially tenacious eczema), bronchial asthma and hay fever, and even a number of cases of essential hypertension, have been relieved by analysis, even after long-attempted orthodox medical therapeutic methods had failed. As he remarks: "Why in 1 case the eventual release of tension leads to hysterical dysfunction of either motor or sensory systems, in another the discharge is localized in that portion of the sympathetic system supplying the thyroid, and in still others it is localized in the gastric portion of the autonomic system, we may not discover The same fundamental tension may be released through any of these channels, and psychoanalysis . . . offers the most thorough method . . . of establishing permanent channels of normal discharge." Analysis enables the individual to relieve tensions in the normal social functions of the total personality which previously secured no discharge and as a result were limited to localized pathologic organic stimulation. The anatomical basis for such an assertion is to be found in the role of the, as yet little understood, autonomic nervous system, to which M. Sakel⁵¹ refers in these terms: "The link between the organic and the psychic part of the human being is the vegetative nervous system In the same way that the vegetative nervous system can translate organic experience into mental response, it can transform psychic stimuli to pathophysiologic expression and, *vice versa*, in a vicious circle."

In conclusion, the psychosomatic viewpoint is well summarized by C. Binger⁵² in his statement "Our changing attitude toward disease is due to a growing body

of evidence which points to the importance of psychic influences in the process of falling ill and to the fact that disease, be it infectious, allergic, functional, organic or degenerative, has its developmental history in which the whole personality is involved." And as W. C. Menninger⁵³ points out: "Disease should always be considered as a psychosomatic reaction. The emphasis may be either on the psychic or the somatic symptoms, but both components are always present."

Treatment in the Psychoneuroses

General Psychotherapy — (1) Die-thelm⁵⁴ emphatically declares that "one should keep in mind that they are disorders of the personality, and not of nervous tissue." The main treatment procedure is therefore *psychotherapeutic*. No purely somatic treatment is justified. Medication helps symptoms only. This contribution explains in clear and precise fashion the necessary essentials in the handling of the milder forms of these personality disorders. (a) The correct procedure through which to obtain a psychiatric history, (b) how to obtain a brief yet workable analysis of the patient's personality, and (c) the various treatment procedures which may be followed after the therapeutic formulation has been arrived at. Many practical suggestions are likewise offered in conducting a therapeutic interview and the therapeutic goal is clearly expressed. The psychotherapeutic method of approach outlined is one for which any general practitioner will find ready use in his routine office practice. As the author concludes "It should be the goal of training during interneship not merely to recognize psychiatric, especially psychoneurotic disorders, but to learn to treat them correctly. The psychiatrist should not be expected to claim all these

patients for treatment. The well-trained internist and general practitioner should be able to treat a considerable number of these cases correctly without special-istic help."

T. A. C. Rennie⁵⁵ scores the frequent tendency in general practice to label these patients as "neurotic" and the subsequent inclination to dismiss these cases as hopeless or hardly worthy of a busy practitioner's time. He points out the dangers of presenting the patient with vague terms, of informing the patient that his "imagination alone" is at fault, or of proffering the mere advice "to forget it all." An easily understandable working concept of the neurotic personality is presented, followed by an effective method for the therapeutic handling of these personalities, entirely on a practical basis, as the author feels that "any state of general nervousness, tension, anxiety, hypochondriasis, or neurasthenia can be adequately and successfully treated by the nonspecialist." Especial emphasis is placed on the advisability of avoiding medications, particularly sedatives, if at all possible. These are regarded as "artificial ways of easing painful symptoms" whose origins are psychogenic. Any medication resorted to needs careful explanation that it is being given only as a means of producing symptomatic and temporary relief, since permanent cure involves a growing insight into the true emotional reasons behind the maladjustment.

G. S. Sprague⁵⁶ purposes "to bring together into clearer focus some principles of the psychiatrist's treatment," especially the underlying reasons for the various forms of therapy. Anyone treating emotionally ill patients must have clear conceptions of what he is trying to accomplish and of the exact means available. The paper contains many worthwhile ideas centering around the thera-

peutic handling of the individual patient's needs.

Anxiety States—The handling of anxiety states in general practice can be facilitated by the suggestions offered by E. Kahn, *et al.*,⁵⁷ who urge the therapeutic approach which keeps in mind the needs of the "whole person" and which looks upon anxiety as a defense mechanism whose protective purpose must first be understood in any therapeutic approach. E. F. Gildea lists 3 different varieties of anxiety which must be differentiated in the therapeutic approach. P. W. Preu's observations are helpful in differentiating anxiety from other states (such as hyperthyroidism, incipient psychoses, etc.), while W. B. Terhune lists practical hints in the direct handling of anxiety conditions, especially the justifiable medicinal handling of acute anxiety (*medinal*, 10 grains (0.6 Gm.); *sodium amytal*, 3 grains (0.19 Gm.), or *nembutal*, 2 grains (0.13 Gm.)—given alone or in a combination of any 2). If the fear of not sleeping tends to increase the anxiety, these patients may be benefited by *medinal*, 5 or 10 grains, 30 minutes before bedtime. This administration may be preceded early in the evening by 15 grains (1 Gm.) of *triple bromide*. The value of *endocrine therapy* remains unproven in these cases. The psychotherapeutic handling of the anxiety reaction is also clearly described. As this contributor points out, the family doctor is the only man who has the opportunity of curing the anxiety state *at the moment* it arises. In this symposium, M. C. Putnam briefly presents the Freudian hypothesis of the anxiety reaction and G. K. Pratt outlines the community aspects of these conditions which must always be kept clearly in mind whenever dealing with the anxiety neuroses.

Traumatic Neuroses — Especially perplexing to the general practitioner is the handling of neurotic reactions to accidents, and even more so when the matter of industrial compensation is at stake. This subject is covered in very practical fashion by A. Myerson.⁵⁸ The law insists that for such cases to be compensable there must have been physical damage associated with the accident. Deep psychic damage is not compensable. The situational nature of the traumatic neuroses is emphasized, as they develop most readily in relationship to litigation and to compensation. Several varieties of these neuroses are listed and some differential points are taken up which enable true malingering to be ruled out. Although most writers seem to agree that prognosis in compensation cases is improved if an early settlement of the case is reached, this writer does not feel that such a procedure in itself ends the symptomatology. Various considerations to be followed in the treatment of these cases are set forth.

Hysteria— A practical approach to the handling of hysterical reactions is illustrated by E. Lindemann.⁵⁹ Management of the case may be along 1 of 3 different varieties of approach. The "explorative" method aims at a thorough rearrangement of the patient's inner phantasy life. This is most efficiently effected by the psychoanalytic procedure. Nevertheless, because of the time and expense factors, this method is rarely feasible. The "environmental" method of handling the case depends on a thorough understanding of the "factors in the patient's environment which set up the stimulus to which the patient's symptoms are the response." Changing these factors may alleviate the symptoms, but the fundamental personality remains unchanged. The "suggestive" method employs direct suggestion in the form of

hypnosis or the more indirect suggestive element residing in electrical treatments, certain kinds of medication, etc. But as stated by the author, when we use suggestive methods alone, we remain ignorant of the factors determining the abnormal response and we do not remove the propensity to further symptom formation.

The fact that hypnosis, as an adjuvant to the psychotherapeutic handling of certain psychiatric conditions, has in the past fallen into general disfavor, is regarded as unfortunate by J. L. McCartney.⁶⁰ Its disrepute has largely been brought about by the fact that hypnosis deals chiefly with symptoms rather than with causes. Nevertheless, although it should not be looked upon as a panacea, this author regards it as a valuable addition to the psychotherapeutic armamentarium. Its special usefulness resides in the fact that hypnosis enables the physician directly to influence the subconscious, permitting him to implant therapeutic ideas; it permits exploratory measures whose findings may be helpful in the psychotherapeutic reintegration of the personality; it increases the receptive state for psychotherapy; and it permits reassociation and reorganization of dissociated experiences and of anmesic material. The mechanism of hypnosis and of normal sleep are held to be the same, and the rapport established between the patient and the physician is compared to the "transference" sought in the usual psychoanalytical situation. A simple technic for the production of the hypnotic state is described and several case reports given to illustrate the surprising and gratifying therapeutic results obtained. Among the conditions either cured or greatly ameliorated in this writer's experience are: amenorrhea and dysmenorrhea; impotence; paralysis; torticollis; insomnia; migraine; alcoholic ad-

diction; constipation; nausea; preparation for anesthesia, and immense reduction in the painfulness of childbirth. The author concludes that hypnosis may be used to facilitate the beginning of mental catharsis, that "it is the best method for the treatment of amnesia . . . and that it may be used to overcome many functional symptoms, and to supplement other forms of psychotherapy."

M. H. Erickson⁶¹ outlines a practical technic for the induction of the hypnotic state. He also recalls how in Germany and France hypnosis has in selected cases been used as a direct surgical aid in both major and minor operations as well as in obstetrics, making for peace of mind, and a sense of security and confidence on the part of the patient.

Alcoholism as a Neurosis—Significant contributions have been made to the treatment of certain forms of alcoholic addiction by Strecker and Chambers. Following the conceptions set forth by Peabody a few years ago, increasing emphasis has been placed upon the theory that certain forms of alcoholism constitute the manifestations of an underlying psychoneurotic personality difficulty. This theme is ably set forth by E. A. Strecker,⁶² and by F. T. Chambers, Jr.⁶³

Strecker emphasizes the point that "without specific psychotherapy there is rarely permanency to the initial good result." The border line to abnormal drinking "is crossed when a man consistently attempts to use alcohol as an aid to adjust himself to reality." True alcoholism is a neurosis, and alcohol, being more or less socially acceptable, becomes a "useful method of escape for the potential psychoneurotic." Among the frequent factors found in the background of the "alcoholic personality" are: a spoiled-child picture fostered by past parental overindulgence coupled

with overdominance; emotional immaturity and general irresponsibility; being a youngest child or an only child; an introverted personality; neurotic tendencies in the parents; financial difficulties. The use of alcohol in these cases serves as a neurotic solution for mental conflict and acts as a compromise solution, in an effort to free the socially inhibited personality from the confines of its immaturity. The alcoholic drinks in an effort to extravert himself.

A basic premise prerequisite to the psychotherapeutic approach to alcoholism is sincerity on the part of the patient and a real desire to be helped, emanating from the patient himself rather than from the advice of someone in his environment. The form of treatment is not psychoanalytical. Its initial objective is an analysis of the original causal factors of the alcoholic addiction, the nature of the previous maladaptations. It includes a large amount of suggestion and the reiteration of certain principles which in aim strive to inculcate a nonalcoholic philosophy of life, and is in effect a kind of reconditioned reflex to alcohol. A good prognosis cannot be given until the patient has proven his every effort to make the alcoholic compromise a conspicuous failure, and until he shows an intellectual and emotional acceptance of his willingness to believe that an arid, nonalcoholic future is imperative, and that the eventuality of partial indulgence, moderate drinking ("social drinking") or some similar compromise is utterly impossible. The co-operative attitude of the patient's family is imperative, but reference is made to the harmfulness of overstrict supervision, spying and any elaborate precautions concerning having alcohol in the home. Any artificiality is to be decried which prevents the patient from fighting his battle on his own terrain in an emotionally mature way.

This form of therapy has given unusually good results in handling the chronic alcoholic in his own environment. Although institutions are valuable for the complications of alcoholism, mere custodial and protective care is utterly inadequate in establishing real lasting cures.

Chambers⁶³ approaches this problem along the same lines. He would be inclined to view the alcoholic as "a student (rather) than as a patient, a student who has failed to pass the final entrance examination into a mature existence. It is up to him to gain insight as to why he failed and how he can succeed." In this connection it is important to let the patient convince the therapist, and incidentally himself, that he is an abnormal drinker. Frequently the alcoholic personality is confronted with sexual difficulties but these are frequently the result rather than the cause of his alcoholism. Though marital discords are frequent, it is usually because marriage enlarges the field of reality and increases responsibility, the very things which the alcoholic was seeking to avoid by his narcotic use of alcohol.

Treatment with Drugs—(Symptomatic Therapy) There continue to appear favorable reports upon the use of *benzedrine sulfate* in states of chronic exhaustion and depression. The results in fatigue and lassitude (*not* due to organic disease) are sometimes spectacular. Depression is relieved, exhaustion may be replaced by exhilaration and by an increased capacity for both physical and mental work. The presence of anxiety, restlessness and irritability constitute contraindications to its use, as well as the existence of hypertension or cardiac disease. The dosage usually advised is from $\frac{1}{2}$ to $\frac{1}{3}$ grain (2.5 mg. to 20 mg.) taken before breakfast. The effects of the drug can almost al-

ways be determined in 1 day. Its continued administration gradually results in lessened efficacy.

Studies by L. F. Woolley⁶⁴ reveal that a number of retarded patients, regardless of diagnostic grouping, can be materially benefited in their feelings of well-being and in their initiative. Lack of response to small doses (up to $\frac{1}{6}$ grain or 10 mg.) administered over a period of from 1 to 3 days, or unfavorable response to small doses should be taken as an indication to discontinue the medication. The drug is not without its attendant dangers, and its promiscuous and uncontrolled use is to be seriously condemned, even in small doses.

E. C. Reifenstem, Jr. and E. Davidoff⁶⁵ have secured good results in using benzedrine sulfate to combat the mild states of depression to which *alcoholics* are inclined following abuse of intoxicants. Dosages of $\frac{1}{6}$ to $\frac{1}{2}$ grain (10 to 30 mg.) per day (given orally) have proved rapidly effective. Several cases of alcoholic stupor were aroused within 30 minutes after 10 to 30 mg. of the drug had been given intravenously. Satisfactory response was also recorded in delirium tremens and early alcoholic hallucinosis. As these investigators remark: "It is open to question whether this drug should be administered to persons who have demonstrated a tendency to addiction by their chronic alcoholic habits."

We are convinced that, in certain persons at least, benzedrine sulfate is habit forming. Mention is made of the occasional appearance of unpredictable untoward effects and of serious toxic reactions (severe anemia, etc.) which make it imperative that the drug never be used without adequate medical supervision. During the year several medical editorials have condemned the increasing use of this stimulating drug by students at examination times, and by

professional people and by members of the laity on their own initiative. Its indiscriminate sale will undoubtedly have to be restricted.

Benzedrine Sulfate in Behavior Problems—Unusually good results from benzedrine sulfate have been obtained by C. Bradley⁶⁶ who used the drug in 30 children presenting various behavior problems such as disturbed school behavior, retiring as well as overaggressive tendencies, all sufficiently serious to make hospitalization necessary. (These resident patients were all under 12 and of normal intelligence.) The changes appeared promptly the first day that benzedrine was given and disappeared coincidentally with its discontinuation. In many of these children a great increase of interest in school material was immediately noted, as well as the appearance of a definite "drive" to accomplish, and often a desire to spend extra time completing additional work. Speed of comprehension and increased accuracy of performance were likewise noted. Most of the children had shown previous conduct disorders. Under the drug half of them became distinctly subdued in their emotional responses, their mood swings having become diminished. Their previous irritability, noisy, aggressive and domineering behavior was replaced by a more placid, easy-going attitude. They showed a widening of interest in their environment and a diminished tendency to be preoccupied with themselves. *Dosage* used varied between 10 and 20 mg. given upon arising. To explain the apparent paradox as to why a drug, known to be a stimulant, should produce subdued behavior in half of the children, the author remarks, "Portions of the higher levels of the central nervous system have inhibition as their function . . . Stimulation of these portions might indeed produce the clinical picture of

reduced activity through increased voluntary control."

Enuresis—Mention may be made of the use of benzedrine sulfate in 2 other conditions with which psychoneurotic tendencies are often associated. M. Molitch and S. Poliakoff⁶⁷ experimenting with 22 boys who were chronic bedwetters, found that in 8 of these patients the enuresis was controlled by giving placebo medication (tablets) at bedtime. Of the 14 who failed to respond, 12 were entirely relieved by being given small doses of benzedrine (ranging between 5 and 25 mg.) nightly. The initial dose given was 2.5 mg. The rationale for this therapy is founded upon the observation that bedwetters are usually very deep sleepers. If by the use of the stimulating drug benzedrine their sleep could be made less deep, it was felt that they would more readily become aware of any urge to void.

Seasickness—Because of the tendency of benzedrine to abolish spasm in the gastrointestinal tract, J. Hill⁶⁸ has used this preparation in dosages of from 10 to 20 mg. to treat seasickness. Unequivocal improvement was noted in 39 per cent of the cases, in a series of 100.

P. Schilder,⁶⁹ investigating the psychological effects of the drug on patients during analysis, has found that benzedrine may bring forward important material in the course of psychoanalytical treatment, as well as being helpful from a symptomatologic point of view.

Narcosis Treatment—In the literature on the narcosis treatment of the affective and other psychoses, occasional mention is made of the successful application of this form of therapy in severe psychasthenic states. Palmer and Braceland⁷⁰ in reporting their signal success with *sodium amytal narcosis* in manic-depressive psychosis and in some cases of schizophrenia mention the case of a

severe compulsion-neurosis aged 43 who was greatly helped by such treatment. M. G. Schroeder in discussing this paper, reports several complete recoveries in neurasthenic patients subject to a modified narcosis using Dial, as well as considerable success using intramuscular sulfur-in-oil injections.

Insulin and Metrazol Shock Therapy—Although at the time of the introduction of *insulin hypoglycemic shock treatment* for schizophrenia 3 years ago there appeared a few reports of its occasional success in severe psychasthenic states, no such references are noted in the recent literature. On the other hand, there have been a few reports of severe psychoneurotic states successfully treated by *metrazol shock therapy*. Among a series of 66 patients (chiefly schizophrenic and manic-depressive psychoses) A. A. Low,⁷¹ reports 3 "nonpsychotic" cases immensely benefited by this form of treatment. One case was that of a severe anxiety neurosis which was restored to health after 5 years' confinement to a state hospital. The second case had suffered from a long-standing conversion-hysteria with many incapacitating motor symptoms and was returned to gainful employment after only 4 treatments. The third case, also a state hospital patient, recovered from a hypochondriasis of 5 years' duration, and returned to her household responsibilities free of her complaints and of her fears.

Histamine Phosphate—W. Marshall and J. S. Tarwater⁷² report definite improvement in 51 per cent of their series of psychotic and psychoneurotic patients treated with *histamine phosphate* (1:1000 solution) given subcutaneously in increasing doses (Initial dose 0.1 cc., subsequent doses being increased by 0.1 cc. at a time until 1 cc. was reached). This treatment, in which histamine injection is regarded as a mild

form of "shock therapy," is still entirely on an experimental basis.

Transfusions—A novel theoretical and practical contribution to the treatment of certain nervous disorders recently has been advanced by S. Brinness,²³ "*mitogenic blood radiation*" as a basis for therapy. It has been known for some time that most chemical reactions are accompanied by the radiation of short ultraviolet rays which also have a stimulating effect on cell division in tissues. Brinness has noted that these radiations are decreased in the fatigue of neurasthenic states, and in certain schizophrenic and depressed states. On the other hand, these radiations are increased in manic excitement. The theory advanced is that blood of intense radiation could be used as a stimulus for reconstructing the organism showing weak radiation. In the reported experiments, 12 patients with weak radiations were transfused with 30 to 40 cc. of blood drawn from patients with strong radiation. Improvement is claimed to have been observed in all of the patients so treated.

Endocrinotherapy at the Menopause—The treatment of psychoneurotic reactions, characterized by anxiety, appearing at the menopausal period, frequently finds in endocrinotherapy a valuable adjunct. Such treatment may likewise abort a developing involutional melancholia if resorted to promptly. The claims regarding the value of endocrine preparations in these states are not in agreement, and the reports frequently conflicting. A comprehensive review of the situation is given by E. Novak⁷⁴ in an article on the menopause. He draws a significant distinction between the treatment of menopausal symptoms and the management of the woman passing through her menopause. He feels that the vasomotor group of symptoms are

the only ones which seem clearly attributable to the hormonal readjustment of the menopause and the only ones warranting endocrine therapy.

The treatment of the many other manifestations he feels should be along psychiatric and general lines rather than through any endocrine approach. The rationale for substitutive endocrine therapy is based upon the fact that at the menopause, because of ovarian atrophy, the amount of ovarian follicular hormone (estrogen; estrone) decreases. There is a coincident hypertrophy of the anterior pituitary with an increased production of its gonadotropic hormone, whose excess is felt to be the cause of the distressing vasomotor symptoms. Resort to substitution therapy using large amounts of *estrone* thus decreases the activity of the anterior pituitary and lessens the production of the gonadotropic factor. Novak states that in evaluating the results of organotherapy, the proper standard should be only the effect obtainable on the vasomotor symptoms, the other symptoms being psychologically produced. In the matter of dosage, no precise rules apply. Best results are obtained from an estrogenic substance in oil (*e. g.*, *theelin*, *amniotin*, *progynon "B"*) injected intramuscularly. The initial doses may vary between 5000 and 50,000 I. U. Little and Cameron⁷⁵ report good results in anxiety states seen in the menopause from the administration of 1000 units of an estrogenic substance twice weekly. On the other hand, T. H. Cherry⁷⁶ used an initial dose of 30,000 I. U. which relieved the flushes, palpitation and restlessness within 48 hours in the majority of his 55 menopausal patients. He then repeated this dose every 2 days until a total of 150,000 I. U. had been given. Following this the patients were carried on an oral

estrogenic preparation given 3 times daily in doses of 750 I. U.

Whereas many authors claim good results for these specific hormonal preparations, Pratt and Thomas,⁷⁷ after treating 200 patients who came with specific menopausal symptoms, claim that "equally good results may be obtained by many agents used empirically." The percentages of patients asserting complete or partial symptomatic relief from parenteral administration of the following preparations, were as follows: those given *theelol*, 64 per cent; *theelin in oil*, 70 per cent; *emmenin*, 75 per cent; *phenobarbital*, 76 per cent; *lactose*, 69 per cent; and *plain oil*, 85 per cent.

Testosterone Propionate—Because the administration of estrone in large doses may bring about a reactivation of the endometrium with subsequent bleeding, Birnberg, Kurzrok and Livingston⁷⁸ suggest the use of *testosterone propionate* (synthetic male hormone) as being equally effective in depressing the anterior pituitary, but without the danger of endometrial reactivity. Average dosage employed was $\frac{1}{6}$ grain (10 mg) twice a week for 6 weeks, then $\frac{1}{6}$ grain (10 mg) once a week for 6 more weeks, followed by a maintenance dose of the same amount given once every 2 weeks.

Surgical Procedures; "Psychosurgery"—Following the partial success obtained by the Portuguese surgeon Moniz a few years ago in altering the mental symptoms of 20 individuals suffering from different psychoses (10 severe agitated depressions, all of which improved; 3 manics and 7 schizophrenics in whom the results were less convincing), Freeman and Watts⁷⁹ report in considerable detail their results in 4 cases of severe psychasthenia (obsessive-compulsive neuroses and obsessive-ruminative states). The results, although not uniformly good, nevertheless per-

mitted much more satisfactory adaptation on the part of these patients to life. These authors emphasize the frequent therapeutic hopelessness of these cases, especially in persons of middle age, and the frequent inclination to suicide. The operation consists in the surgical interruption of nerve tracts in the subcortical white matter of the frontal lobes of the brain. Using a "leukotome" inserted through small trephine holes, from 3 to 6 small balls of white matter are cut away and left in place, the nerve pathways being thus severed. It is felt that the increased mental comfort which these patients experience is due to a reduction in the emotional charge (affect) of their ideas. The intellectual faculties do not seem to become affected to any serious degree. Though some of the objectionable ideas persist, and some of the

compulsions likewise, their obsessive character is lost, and pathological self-consciousness is overcome, making for considerable relief. In some cases the patients have been able to resume productive activities. The operators feel that they are able to rule out the question of operative shock or of suggestive therapy as acting in these cases, and conclude that "the progressive improvement over a period of months seems to indicate that once the vicious circle is broken through by operation, a progressive readjustment of the whole personality is possible." In Freeman and Watts'⁸⁰ "psychosurgical" handling of 25 psychotic cases, no new psychotic symptoms developed. The only untoward results consisted of 1 death from cerebral hemorrhage and 1 postoperative brachial monoplegia.

SCHIZOPHRENIA

By FRANCIS J. BRACELAND, M.D.

Once more research work in schizophrenia is tending toward the organic side but in addition observers are calling attention to the necessity for psychotherapy at regular intervals during shock treatment. Investigators have amplified the original methods and literally hundreds of articles on schizophrenia have emanated from clinics of Europe and North America. It is a difficult task to separate the chaff from the wheat for, unfortunately, some workers have arrived at conclusions which are based on an insufficient number of cases. Valuable contributions were made at the eighty-ninth meeting of the Swiss Psychiatric Association held in Berne, Switzerland, in May of 1937.⁸¹ A complete transcript of the entire proceedings was published in English as a supplement of the May,

1938, issue of the American Journal of Psychiatry. This may be considered the best condensation of foreign reports for that period.

Insulin is the method of choice in many clinics while others prefer *metrazol*. Most clinics use both agents and select the 1 which seems to be indicated in the case in question. It is most difficult to collect statistical information as to the value of these drugs. This is because the duration of illness has been considered differently and some investigators even omit consideration of it at all. Furthermore the concept of schizophrenia differs in various countries and this adds to the difficulty in making proper evaluation of results.

As a rule the reports from the clinics using shock therapy have been favorable.

There have been dissenting notes from the psychiatric clinics at Wilno (Poland), and from Oslo (Norway), and sporadic ones from a few others. However, it is safe to say that the remission rates under insulin therapy are at least twice as great as was formerly noted under ordinary hospital care without special therapeutic procedures. It is probable that the remissions which take place under insulin therapy are qualitatively superior to the so-called spontaneous remissions.

In a series of 475 cases collected from 22 institutions in Switzerland, where diagnostic criteria is uniform, it appears that paranoid patients do best under insulin therapy. This is particularly true if the duration of the illness is less than 1 year. Catatonic excitement cases follow the paranoid ones, while catatonic stupor cases remain somewhat below the average remission rates. The hebephrenic cases and those with indefinite diagnoses lag far behind the others. M. Muller notes that out of 700 cases which he investigated there were 7 fatalities, a mortality rate of 1 per cent. In Switzerland the rate was still lower with only 2 deaths in 560 patients treated. It is doubtful whether 1 of the deaths resulted from the treatment and therefore the Swiss mortality rate was 0.5 per cent.

Permanent injuries have resulted, but these are really rare. As a sequel to prolonged shocks, Korsakow-like dementia has been reported but it receded after some time. It is believed that some of the accidents could have been avoided.

The investigators are dividing into 2 groups, 1 of which would standardize the treatment because they believe the experimental period is over. The other group tends toward greater individualization of treatment, taking into consideration the characteristics of the

individual patient and trying to modify and improve the treatment accordingly.

Bolles, Rosen, and Landis,⁸² report on what may later prove to be a good prognostic indicator. Through a series of sorting tests administered to schizophrenic patients about to undergo insulin treatment they noted that patients who did poorly in test performances before insulin therapy did not improve under treatment. Those with good performance tests showed most improvement. Only 19 patients were examined and no definite conclusions can yet be drawn. It is plain to be seen that if this work is substantiated a good prognostic indicator is at hand.

Fundamentally, the technic of insulin therapy has not changed in the past 2 years. The use of camphor as a convulsant has been largely discarded in clinical practice because of the difficulty in determining the proper dosage. Metrazol is a much more consistent agent and is soluble in water and readily absorbed. It is the opinion of investigators that the drug has no injurious effects upon the heart. Electrocardiograms are being made upon patients in many clinics and soon enough evidence will have been collected for us to speak with authority upon this particular point.

The metrazol treatment is usually carried out in the morning, and breakfast is withheld. It is well to keep the patient without sedatives because sedatives frequently abort the convulsions. Von Meduna⁸³ recommends the use of a 10 per cent solution of metrazol (pentamethylenetetrazol) and usually begins with 5 cc. Ordinarily, the convulsion occurs at once. As long as the amount suffices and a convulsion results, the dosage is not increased. If the patient develops a tolerance the dosage is increased by 1 cc. at each treatment; in some cases as much as 15 cc. have been given. Ordinarily

patients are treated twice weekly but some clinicians, notably Friedman⁸⁴ treat the patients every second day

At first the convulsion is tonic in character but within a few seconds it becomes clonic. There is always a tonic yawning movement before the onset of the convulsion and this allows time for the insertion of a gauze pad which protects the patient's mouth. Like epileptic convulsions the metrazol convulsions are accompanied by aura and automatisms. During the convulsion the pupils are dilated and fail to respond to light. There is also a positive Babinski. After the convulsion most patients are confused and dizzy and fall into a deep sleep which lasts for 5 or 10 minutes. They regain consciousness and complain of fatigue and exhaustion, and usually fall asleep again. After 5 or 6 hours they have apparently recovered and are allowed to take food and move about.

The number of shock treatments given is an arbitrary one and varies with the individual patient. Some patients respond after the first few treatments while others require as many as 25. Von Meduna believes that even though the patient has apparently had a remission it is well to give 3 more convulsions in spite of this. Thousands of metrazol shocks have been given without very serious complications. Dislocation of the shoulder and dislocation of the jaw are sometimes reported.

Von Meduna's remission rates can be said to roughly approximate 50 per cent. If we consider patients whose illness is less than 1 year's duration the figures rise as high as 90 per cent. His work has been corroborated by many investigators. Finkleman, Steinberg, and Leibert⁸⁵ of Elgin, Illinois, reported on the treatment of 66 schizophrenic patients with metrazol and noted remissions in 85 per cent of the patients whose illness

was less than 6 months in duration. Catatonic patients apparently respond best to metrazol therapy and the paranoid type follows closely.

Himwich, Alexander, and Lipetz²² reported on the treatment of schizophrenia by the *inhalation of nitrogen*. This is a new and interesting method of approach. They base their work on the assumption that in shock therapy there is a common factor no matter what the agent. They say that this factor is diminished cerebral metabolism. In hypoglycemia this factor arises owing to an acute deprivation of glucose, and in metrazol because of an acute anoxemia arising from severe convulsion and temporary interference with respiration. They assume that if the benefit derived from metrazol is due to decreased cerebral metabolism following anoxia, then methods of producing anoxia can be found which would be safer and less strenuous.

Their method of attaining anoxemias consists of having the patient breathe in an atmosphere of pure oxygen which is slowly replaced by nitrogen. An apparatus, consisting of a snug facial mask with an exhalation valve, and container of soda lime, and a 5-liter breathing bag connected in series, is used. The mask is filled with oxygen and adjusted, then nitrogen is slowly introduced to replace the oxygen. The carbon dioxide is absorbed by the soda lime and this decreases the patient's discomfort. At the height of the treatment the patient is breathing almost pure nitrogen. After the signs of anoxemia have appeared the patient is carefully watched and gradually pure oxygen is reintroduced. The patient immediately returns to consciousness. Thus far only 7 patients have undergone treatment. The therapy lasts for 2 to 4 months with 3 sessions a week.

They have noted no complications except headache. The authors say that this method insures a greater depletion of oxygen saturation than does metrazol. despite the great anoxemia attained in this method the patient is under the control of the operator. Obviously this treatment is too new to evaluate as yet, but it does open another new vista to us.

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DISEASES OF THE RESPIRATORY TRACT

By FRANK WALTON BURGE, MD

PNEUMONIA

Etiology

The Massachusetts Pneumonia Program—H D Chadwick¹ gives the following as the 6 commonest types of Pneumococci found in the examination of 9737 specimens from patients with respiratory disease

Type	No. of Cases
I	1485
III	1022
VIII	496
II	378
V	284
VII	238
Total	3903

Occurrence of Different Types of Pneumococci in Cases of Acute Pneumonia in Stockholm—S Gard, G. Lofstrom, and G Jacobsohn² have not been able to confirm Gundel's theory that the pathologicoanatomic aspect of pneu-

monia is determined entirely by the serologic type of the pneumococci. Other factors play just as important a part. It is not justifiable to ascribe any special position to Types I and II. However, Type I predominates in the frequency statistics but several of the other types have proven capable of causing pneumonia with as high or higher a mortality rate.

Gundel's assumption that dissimilarities in the mechanism of infection (exogenous or autogenous) is the decisive mortality factor cannot be accepted as satisfactory. Approximately half of the lobar forms of pneumonia are caused by pneumococcus Type I, so that the production of Type I serum for therapeutic use must be regarded as one of the most important means of reducing mortality from pneumonia. The next step would be to make serum against II and VII. The experience abroad with serum of

these 3 types of pneumococci has been extremely favorable.

Type I *Pneumococcus Pneumonia*: **Observations from Study of 2000 Cases Treated with Specific Serum**—E. S. Rogers and M. E. Gooch³ believe that sex does not influence the mortality, except through its relationship to pregnancy. Pregnancy is a factor predisposing to pneumonia.

Pneumonia Due to Type V *Pneumococcus*—M. B. Rosenbluth and M. Block⁴ found 68 cases of pneumonia due to Type V pneumococci among 1850 cases of pneumococcic pneumonia, an incidence of 3.5 per cent. There is a tendency to epidemicity, as groups of 4 to 5 patients have on several occasions been admitted to the hospital within a few days.

Type V pneumococci, in contrast to many of the new types of pneumococci, rarely, if ever, occur as saprophytes in the mouths of normal persons. It was not found in any case, except in association with definite pneumonia.

Predisposing factors seem to be similar to those found in other types of pneumonia. A predominant factor is infection of the upper respiratory tract, usually a common cold, as was present in 34 of the 68 cases. Twenty gave a history of exposure; 2 gave a history of trauma; 3 of alcoholic stupor; and 3 of dietary deficiency. In 3 cases, pneumonia was associated with pregnancy. In 1 case, pneumonia developed while the patient was in the ward and definite contact infection was evident. Only 7 of the 68 patients were women. The ages of the patients were scattered fairly evenly, except that there were 24 patients in the fourth decade.

Necropsy Evidences on Relation of Smoky Atmosphere to Pneumonia—S. R. Haythorn and H. B. Meller⁵ reviewed the evidence accumulated and

added to it the data required through the analysis of 3000 persons dying from various diseases in Pittsburgh hospitals. The examinations were made for the purpose of determining the kinds and extent of the changes in the lungs and the amount of visible deposits of dust. The series represents a cross section of the general inhabitants of the city of Pittsburgh.

The lungs removed at necropsy were graded microscopically for the amount of extraneous pigment and the resulting fibrosis. Grades 0, 1 and 2 appeared to have no particular occupational basis. Grade 3 was a mixed nonoccupational and occupational group. Grades 4 and 5 were largely, although not exclusively, occupational.

The incidence of pneumonia of all forms and of lobar pneumonia was tabulated in relation to each grade of anthracosis. In spite of the high local death rate from pneumonia, no anatomic evidences of a relation between the incidence of pneumonia and the milder grades of anthracosis could be demonstrated in the nonoccupational groups. In grades 3, 4 and 5, there was a definitely higher percentage of pneumonia, but the average age for each of these grades coincided with the period of life at which the death rate from pneumonia in less smoky communities is likewise highest.

Healing by organization of unresolved pneumonia was consistently higher in all of the more advanced grades of anthracosis and greatest in grade 5. The organizing foci appeared to be associated with heavy deposits of pigment, microscopic areas of fibrosis and isolated emphysematous pockets in fibrosed portions of the lungs. Nothing tangible was found to connect the deposits of pigment with the high incidence of pneumonia and high mortality rates, but the association

of severe anthracosis and healing by organization is verified.

Symptoms

Pneumonia Due to Type V Pneumococcus—M B Rosenbluth and M. Block⁴ state that symptoms such as headache, vomiting, and jaundice are common

Clinical Course—The clinical course was characterized by an abrupt onset and a prolonged course, and in more than half of the cases there was termination with crisis

Investigation on Vitamin A in Pneumonia—T. Lindquist⁶ investigated the vitamin A content of the serum of 45 patients with pneumonia The carotinoids and the vitamin A was extracted from the serum by the method recommended by van Eekelen and Emmerie The carotinoid and vitamin A content was low during the course of the pneumonia A tabular report indicates that in all but 6 of the patients the values were below the normal average

These low values exist during the first few days of the pneumonia During the convalescence the values increase rapidly without vitamin A being added to the diet One week after the crisis the vitamin content is usually 3 times as high as before the decrease in temperature There is no storage of vitamin A in the diseased lung The cholesterol content of the serum is considerably decreased, but this is not responsible for the disturbances in the vitamin A content During the fever period, large quantities of vitamin A are eliminated in the urine

The vitamin A content of the liver is in most cases considerably reduced, but there are also cases in which the values are high Under pathologic conditions the vitamin A content of the serum is not a reliable measure for the vitamin standards of the organism The low vitamin A content of the serum of patients with pneumonia is partly the result of excessive elimination in the urine Moreover, the mobilization of the hepatic stores may be difficult It was impossible to determine to what extent a low vitamin content was present before the development of the pneumonia

Complications

Pneumonia Due to Type V Pneumococcus—M B Rosenbluth and M Block⁴ frequently found complications in Type V pneumonias There was a high incidence of bacteremia and anoxemia

The Massachusetts Pneumonia Program—H D. Chadwick¹ believes it is important to take a blood culture on every pneumonia patient to determine whether bacteremia exists In such cases, larger doses of serum are necessary

Blood cultures were done on 635 (47.4 per cent) of 1341 cases of Types I, II and V pneumonia About 26 per cent of Type I, 29 per cent of Type II and 24 per cent of Type V cases showed positive blood culture results

The following table of Type I and II Cases with and without bacteremia treated with serum shows the fatality rate is high for cases with positive blood cultures:

	Type I			Type II		
	No of Cases	Deaths	Fatality Rate	No of Cases	Deaths	Fatality Rate
Negative	340	28	8.2%	113	17	15.0%
Positive	112	32	28.6%	47	22	46.8%

The following table of fatality rates of cases of pneumococcus pneumonia in different age groups, listed according to the presence or absence of bacteriemia, shows a higher fatality rate in the older age group, and suggests that the incidence of positive blood cultures increases with age.

	0 to 49 Years of Age			50 Years and Over		
	No of Cases	Deaths	Fatality Rate	No of Cases	Deaths	Fatality Rate
TYPE I						
Negative	290	17	5.9%	49	11	22.4%
Positive	85	18	21.2%	27	14	51.8%
TYPE II						
Negative	87	8	9.2%	25	9	36.0%
Positive	34	13	38.2%	13	9	69.2%

Pneumonia Mortality and Treatment of Rickets—U Gruninger and W. Droste⁷ point out that the death rate from pneumonia is comparatively high in children during the first year of life. Nevertheless, at the children's clinic in Dusseldorf, a noticeable decrease in the mortality from pneumonia has been observed during recent years.

Analysis of 1645 cases treated during the years 1924, 1926, 1928, 1930, and 1936, reveal considerable differences in the mortality in the various types of pneumonia.

Uncomplicated lobar pneumonia of 1 lobe, heals with or without treatment.

In all pneumonia, exclusive of the lobar pneumonias and the abscess-forming pneumonias, the nurslings with rickets have a higher mortality rate.

Fresh air treatment produces a noticeable decrease in the mortality of different types of pneumonia. In the whooping cough pneumonias and in the complicated bronchopneumonias, the favorable effects of fresh air treatment can be increased further by the viosterol treatment of the children with rickets. Massive

doses of viosterol D₂ are of value in treating rachitic children with pneumonia.

Diagnosis

The Massachusetts Pneumonia Program—H. D. Chadwick¹ reports that during the latter part of the pneumonia study, the coincidental develop-

ment of the Neufeld method of typing pneumococci in the sputum provided rapid and simple laboratory procedures.

The introduction of the Neufeld method furnished the key to the problem of controlled serum distribution in that it made it possible to restrict the distribution of serum to those who might reasonably be expected to profit from its use. Such a limitation was essential if so costly a serum was to be distributed at public expense. Experience extending over 2 years has proven the administrative plan to be sound.

Unusual Physical Signs in Lobar Pneumonia—G. S. Erwin and R. J. McGill⁸ state that lobar pneumonia may present, in place of the classic physical signs, abnormal signs confusing the diagnosis even when the onset, symptoms and temperature all seem conclusive. The explanation of these perplexing features can be found only in the physiologic and pathologic changes in the underlying lung, since physical signs in themselves, even when taken in groups, are not conclusive proof of any particular disease. Thus the consolidation of pneumonia due

to alveolar exudate is usually evidenced by dullness to percussion and by bronchial breathing, and these are the accepted signs of the disease. When alveolar exudation is complicated by bronchial filling there is produced a different group of physical signs—those of a solid lobe with a blocked bronchus. A complete absence of breath sounds is discovered, together with other signs suggestive of a moderate accumulation of fluid.

Urinary Excretion of Pneumococcus Polysaccharide in Lobar Pneumonia—R Cruickshank⁹ points out that the specific polysaccharides of Types I, II and III pneumococci are excreted in the urine of the majority of patients with lobar pneumonia due to these 3 types and may be demonstrated by a precipitation reaction. This urinary precipitation test has only a limited value as a method for the early serologic typing of lobar pneumonia, as the first specimen of urine examined was positive in only one-fifth of the Type I and one-half of the Type II infections. The detection of the polysaccharide in the urine early in the infection has, however, a grave prognostic significance, since the mortality in such patients was around 40 per cent, whereas less than 2 per cent died whose urinary specimens were persistently negative. The pneumococcus specific substance continues to be excreted in the urine during the patient's convalescence and in explanation of this phenomenon it is suggested that the polysaccharide as an antigen is gradually dissociated from the antibody and slowly excreted by the kidneys.

Differential Diagnosis

The Massachusetts Pneumonia Program—H. D. Chadwick¹ states that there has been a steady increase in the

demand for pneumococcus typing since the program started.

By 1934, a review of the experience of the State bacteriological laboratory with the then new Neufeld method of typing showed it to be simple, rapid, and reliable. The time required for typing was reduced in most instances from many hours to a few minutes.

During the study, typing was carried out on nearly 10,000 specimens obtained from patients with lobar pneumonia or bronchopneumonia, and in a few instances from those with other varieties of respiratory disease. If all specimens had come from patients with lobar pneumonia, undoubtedly a larger percentage of Type I and Type II pneumococci would have been found. The six commonest types of pneumococci found in this large group were Types I, III, VIII, II, V and VII, in the order named. These were found in 41 per cent of all specimens examined, or 67 per cent of all specimens containing pneumococci which could be typed.

Disseminated Focal Pneumonia—J. G. Scadding¹⁰ encountered 4 cases of acute or subacute pulmonary infection which seem to form a recognizable clinicoröntgenologic group, important because of the unusual and possibly prolonged course and the resemblance of the x-ray changes to those of pulmonary tuberculosis. The clinical and x-ray evidence suggests that the pulmonary lesion in these cases was essentially a pneumonia in small foci disseminated through lobes or parts of lobes of the lungs and liable to enter on a phase of delayed resolution. There arises the concept of a process characterized by pneumonic consolidation in small scattered foci; the individual foci at any time may be of different ages and at different stages of evolution toward resolution, organization or suppuration. They may clear

almost completely or may leave more or less residual fibrosis. The process shows little of the tendency to a clear-cut termination seen in the more usual types of pneumonia, and may enter a subacute or chronic phase. If a case presenting this picture comes to necropsy, there will be little that is striking to the pathologist except the focal distribution of the lesions; the main interest of the picture is clinical. The symptoms differ clinically from those of other forms of pneumonia in several respects. The onset was not sudden, as in lobar pneumonia, and there was no evidence of a previous descending infection of the respiratory tract. The initial symptoms were mostly constitutional—malaise, headache, sweating, and shivery sensations short of an actual rigor. Cough, at first dry, subsequently became productive of increasing amounts of purulent sputum, reaching a maximum after several weeks and continuing thereafter according to the progress of the case. Defervescence occurred in the fourth or fifth week, and symptoms, especially cough and sputum, continued for another week or 2. The physical signs were most evident over the upper lobes in 2 cases and over the lower lobes in 2. They consisted of moderate impairment of percussion note, weak breath sounds and numerous fine to medium rales. No definite consolidation signs were detected. Roentgenologically the picture consisted of areas of diffuse, rather coarse mottling, in foci varying from about 2 to 5 mm. in diameter. These changes were confined to the left upper lobe in one case and affected parts of more than 1 lobe in the rest. Resolution was slow in all but 1 case, in which it was not complete for at least 12 weeks from the onset. The resemblance of the infiltration to that of tuberculosis was at times striking. The most remarkable feature of the bacteriol-

ogy of the sputum in these 4 cases was the absence of organisms usually associated with pneumonia. Only organisms that might be found in any respiratory tract were isolated. The etiology remains obscure. The existence of the syndrome calls for caution in the application of collapse therapy in cases in which pulmonary tuberculosis of acute onset is suspected on x-ray grounds without confirmation from bacteriologic examination.

Occurrence of Different Types of Pneumococci in Cases of Acute Pneumonia in Stockholm—S. Gard, G. Lofstrom, and G. Jacobsohn² point out that the type differentiation of the pneumococci has opened up fresh avenues of approach for the study of the epidemiology and therapy of the pneumococcal infections.

The sharp line of distinction between croupous lobar pneumonia and catarrhal bronchopneumonia cannot be maintained. Acute pneumonia presents varying pathologicoanatomic appearances ranging from the fibrinous, lobar form, passing gradually into catarrhal bronchopneumonia and showing intermediary and mixed forms with variations in regards to the abundance of fibrin and the lobar dispersion. The pathologicoanatomic diagnosis made on the basis of clinical and roentgenologic observations is of value in determining the prognosis, and its importance is enhanced if it is supplemented by a bacteriologic investigation, which, moreover, is absolutely essential as a preliminary to a specific therapy.

Prognosis

The Massachusetts Pneumonia Program—H. D. Chadwick¹ gives the following figures as the average annual death rates per 100,000 population of pneumonia in Massachusetts:

Years	Pneumonia (all forms) mortality
1856-1865	107.4
1866-1875	132.2
1876-1885	150.1
1886-1895	180.7
1896-1905	174.7
1906-1915	174.1
1916-1925	164.8
1926-1935	99.1
1936	96.3
Percentage decline, 1856-1936.	10.3

The fatality rate of serum-treated Type I cases has been a little higher since January 1, 1938. Blood culture studies in the group suggest that possibly the pneumonia was of a more severe form than in previous winters. This may in part explain the increase in mortality. Also, more physicians are using serum and many of them have not had the experience necessary to employ it most effectively. Possibly, the higher fatality rate of 14 per cent in Type I cases during the past 12 months is a more accurate index of what the general practitioner may be expected to accomplish with serum than was the previous figure of 10 per cent, which was based on treatment of cases by a selected group of physicians who had previously been instructed in serum therapy.

When physicians as a class become experienced in the use of serums, it is not too optimistic to forecast a reduction of at least one-half in the case-fatality rates of Types VII and VIII pneumonias.

Control

The Massachusetts Pneumonia Program—H. D. Chadwick¹ reports that the Massachusetts pneumonia study had 2 objectives:

1. The evaluation of pneumonia serum under the conditions of the general practice of medicine;
2. The development of plans for the distribution of this serum for the treat-

ment of those patients to whom it might be of benefit.

The following are the purposes of the Plan:

1. To study the epidemiology of lobar pneumonia in the State;
2. To promote more prompt diagnosis of the disease;
3. To encourage and facilitate earlier and more general serum treatment;
4. To study and improve methods of serum production;
5. To correlate the studies on serum production with the results following its clinical use;
6. To devise procedures for the future prevention, serum treatment, and control of the disease.

Community Provision for the Serum Treatment of Pneumococcic Pneumonias—R. L. Cecil, J. G. M. Bullowa, H. T. Chickering, E. H. L. Corwin¹¹ report that during the next few years, departments of health should engage in a vigorous campaign against pneumonia. Special divisions of pneumonia service should be established under the guidance of properly qualified physicians.

Through the regular medical channels, physicians should be made cognizant of the fact that serum is life saving in certain types of pneumonia and the specific type pneumonia from which the patient is suffering should be determined at the earliest possible moment. Free facilities for the rapid determination of the type of infection should be made available in each community at all times, day and night.

Because of the communicable nature of the pneumonias, it is highly desirable that pneumonia patients in hospitals be segregated in cubicles and that a complete aseptic technic be followed.

Pneumonia patients should be considered in the same urgent category with

emergency surgical cases. Certain physicians on the attending staff should be made responsible for the treatment of these patients and should be on call day and night, as is the custom in the surgical services.

In connection with the divisions of pneumonia service of health departments, a clinical consultation service should be established to aid physicians in the administration of serum therapy and in the taking of specimens of blood and sputum for bacteriologic study.

In all instances of death from pneumonia, physicians should be requested to report the bacteriology of the invading organism

Treatment

Sulfapyridine* — During the past year there have appeared in the British and American literature encouraging reports on the use of sulfapyridine (M & B 693) in the treatment of pneumococcal infections. The available laboratory^{12, 13, 14, 15} and clinical^{16, 17, 18} data suggest that this new chemotherapeutic agent is highly effective against the pneumococcus, and there is reason to believe that it will find widespread use in the treatment of pneumococci pneumonia. Most of the clinical reports have stressed the frequency in which the initiation of drug treatment is followed within 24 to 36 hours or less by a critical drop in temperature. This temperature drop is not immediately accompanied by any significant change in the lung signs but always reflects a marked improvement in the toxemia and general well-being of the patient. Resolution of the pneumonia then follows within a variable period of days, although we cannot say whether resolution is hastened or retarded by the fall in temperature. The critical drop

in temperature is followed within 12 to 24 hours by a marked drop in the total leukocyte count. This we believe represents a favorable sign, as in cases where the white blood count remains elevated, despite adequate drug therapy, the usual clinical improvement is retarded. In some instances there is a recurrence of low grade fever which persists for several days after the initial critical drop. From the reports in the literature and personal communications the mortality rate in sulfapyridine treated cases is about 7 per cent.

As with any new therapeutic agent certain points should be made about its mode of administration, dosage and toxic effects. At this time there are no definite rules as to the amount of drug that should be given. This is partly due to our inability to predict what constitutes an effective blood level of sulfapyridine in patients with pneumonia. Experience thus far fails to show any correlation between the blood sulfapyridine level and the therapeutic effect. In elderly individuals and in young persons with renal impairment we find that the blood levels are uniformly high. On the basis of our experience and that of others we are adhering to the following dose schedule in adult patients. An initial dose, by mouth, of 2 Gm followed every 4 hours by 1 Gm until the required total dosage as outlined below is given.

- 1 Patients treated during the first 5 days of the disease receive a total of 25 Gm.

- 2 After the fifth day 15 Gm is sufficient in most instances.

- 3 All cases of bacteremia should receive at least 25 Gm and usually more, sometimes a total of 50 Gm is necessary.

- 4 In elderly patients and those with renal involvement a total dosage of 15 Gm. will often suffice.

*Based upon treatment of 350 cases by Harrison F. Flippin, M.D., Philadelphia.

5. When there is evidence of spread in the pneumonia, despite a normal temperature, a larger total dose is advisable.

6. In cases where specific serum has been used without apparent success sulfapyridine should be given as outlined above.

7. The failure of a patient to show clinical improvement after 48 hours of adequate sulfapyridine therapy is considered by some an indication for specific serum. So far our experience with this form of treatment is limited as we have had but several occasions in which to test its real value.

In the treatment of infants and children we have been giving $1\frac{1}{2}$ grains per pound of body weight every 24 hours in divided doses. The total dosage in this age group has varied with the individual case.

Toxic Effects—As with sulfanilamide, the toxic effects of sulfapyridine are sufficient to require close observation of the patient and careful usage of the drug. The most troublesome and most frequent untoward effects of the drug are nausea and vomiting. Both are most likely to appear during the first 24 hours of treatment and are probably of central origin rather than local gastric irritation. The following methods have been used to control the nausea and vomiting and in individual cases each of these adjuvants appear to improve the tolerance for the drug.

1. The administration of small amounts of sodium bicarbonate after ingestion of the drug.

2. Mixing of the drug with water, fruit juices, or milk.

3. Omission of treatment for 1 or 2 doses, followed by its resumption.

4. The use of barbiturates and chloral hydrate often brings relief.

5. The introduction of sodium chloride and dextrose intravenously is ad-

visable in all patients who show nausea and vomiting. This appears to be a valuable method of minimizing these symptoms as well as of restoring normal fluid and electrolyte balance in the patient who is vomiting.

The extreme insolubility of the drug has made impractical its administration through the rectum. We have tried unsuccessfully the use of an enteric coated tablet by mouth. The other toxic reactions which we have observed or have been reported include cases of transient hematuria, dermatitis, acute hemolytic anemia, leukopenia, drug fever, and agranulocytosis.¹⁹ Cyanosis does occur but its presence does not necessitate the withdrawal of the drug. It seems that aside from the nausea and vomiting these toxic reactions do not occur as frequently with sulfapyridine as with sulfanilamide.

In view of the above toxic effects it is advisable to watch the urine closely for red cells, acetone and urobilin, and the blood count for signs of progressive anemia and neutropenia. In elderly patients the blood urea nitrogen level should be checked and in those with severe vomiting blood chloride studies are indicated.

The Massachusetts Pneumonia Program—H. D. Chadwick¹ reports that the demand for therapeutic pneumonia serum has increased since the latter part of 1935, by which time serum was available on an equal basis to all physicians in the State of Massachusetts.

The fatality rates for cases treated with specific serum in the early part of the Massachusetts study and the results reported elsewhere in this country clearly showed that the maximum benefit of serum treatment was obtained when the treatment was begun within the first 4 days of illness, and further that the serum then available was useful for treating only Type I and Type II cases.

It was decided to broaden the scope of the plan and inform all physicians that under certain conditions they could obtain serum from the laboratory of one of their nearby hospitals where there was a technician who had qualified in

pregnant or had been delivered within the previous 7 days.

The fatality rates of cases of pneumococcus pneumonia treated with concentrated serum within 96 hours of onset, and those not given serum are:

	No. of Cases	Deaths	Fatality Rate
TYPE I			
Treated With Serum*	1043	145	13.9%
Treated Without Serum**	1614	403	25.0%
TYPE II			
Treated With Serum*	281	63	22.4%
Treated Without Serum**	992	407	41.0%

* Massachusetts Pneumonia Study cases from January, 1931, to June 30, 1937.

** Cases collected from the American and Canadian literature, 1912 to 1933.

pneumococcus typing at the State laboratory. These conditions were:

1. Sputum or other material from the patient shall first be typed and shown to contain Type I or Type II pneumococci.

2 The physician must be willing to certify that his patient has not been ill with pneumonia longer than 4 days (96 hours).

3 The physician must agree to fill out and return to the Department, when his patient is discharged a brief questionnaire which will be furnished him with the serum.

Upon meeting these requirements, physicians would receive an average dose of serum, or 60,000 units for Type I cases and 100,000 units for Type II cases

Provision also was made to distribute an additional amount of serum to any patient whose temperature failed to fall below 101° F. (38.3° C.) by mouth within 18 hours of beginning treatment, or, if having fallen, it rose above this level within 48 hours. The extra amount of serum was also made available for patients having a pneumococcus Type I or Type II bacteriemia, or who were

The following table gives data on Type I cases treated with serum as to the number and percentage of deaths by day on which serum treatment was begun:

Serum Treatment Begun	No of Cases	Deaths	
		No	Per-centage
1st Day	183	26	14.2
2nd Day	384	42	10.9
3rd Day	294	40	13.6
4th Day	182	37	20.3
Totals	1043	145	
Average			13.9

Since the beginning of 1938, serum has been distributed for Type V cases. The few cases that have been treated thus far have responded very favorably

The following table illustrates the fatality rates of Type V Pneumococcus pneumonia cases treated with concentrated serum within 96 hours of onset and those not given serum.

	No of Cases	Deaths	Fatality Rate
Treated With Serum*	17	1	5.9%
Treated Without Serum**	337	109	32.4%

* Massachusetts Pneumonia Study cases

** Cases collected from American literature

The importance of the administration of pneumonia serum early in the course of the disease cannot be overemphasized. The policy until recently has been to distribute serum only for use in patients who had not been ill more than 4 days. However, investigation has proven that although serum treatment is begun later than 4 days, it may in some instances save lives. Therefore, the plan has been modified, and the serum is available for any case of pneumonia of the right type, regardless of the length of time the patient has been ill.

Of 1341 Types I, II and V cases, 326 (24.3 per cent) were treated at home.

Serum Dosage—At least 60,000 units should be administered for all Type I cases and 100,000 units for those of Type II, and additional doses of from 40,000 to 60,000 units at 3- or 4-hour intervals for all patients with bacteremia, pregnancy or who have been delivered within 7 days, are 40 years of age or over, have involvement of more than 1 lobe, or whose treatment was begun on the fourth day of the disease or later. Similar extra doses are advised when the temperature does not fall below 101° F (38.3° C) by mouth (102° F or 39° C by rectum) within 18 hours of beginning serum treatment, or when the temperature rises above that level within 72 hours after the initial drop.

In the first 5 years of the pneumonia study, serum was used by about 387 physicians. Since then, in a period of about 18 months, approximately 1100, or about 1 in 6 of the total number, in the State of Massachusetts have used serum therapy.

In the near future, serums for Type VII and Type VIII infections will be ready for distribution. This will bring the number of therapeutic serums up to 5 specific types of pneumococcic serums

available to physicians in Massachusetts without cost to their patients.

Type I Pneumococcus Pneumonia: Observations from Study of 2000 Cases Treated with Specific Serum—E. S. Rogers, and M. E. Gooch³ treated 2027 cases of Type I pneumococcus pneumonia with concentrated Type I antipneumococcus horse serum.

The mortality rises in direct relation to the duration of the disease at the time treatment is started. Five hundred and forty-four patients were treated on or before the fourth day of illness and the fatality rate was 15.8 per cent. One hundred and eighty-three patients received treatment later than the fourth day of illness and the mortality rate was 33.9 per cent.

Of the 544 patients, 251 received less than 100,000 units of serum and 17.5 per cent of them died, 293 received 100,000 units or more and 14.3 per cent of them died. This does not seem favorable to large dosage but of the 293 patients, only 66 of them received all of their serum within a 24-hour period. Of these 66 patients only 6.1 per cent died, while of the 227 patients who received a similar amount of serum over more than 24 hours, 16.7 per cent died.

The use of Type I serum in the treatment of improperly typed cases, untyped cases or cases of heterologous types is not advisable. Of 129 such treated cases, the crude case fatality was 28.6 per cent.

Pneumonia Due to Type V Pneumococcus—M. B. Rosenbluth and M. Block⁴ found that in Type V pneumonia cases in which serum treatment was given, there was a lower mortality than in those cases in which serum treatment was not given. The difference was especially marked when treatment was given early in the disease.

Bacteriologic Etiology of Bronchopneumonia in Infants—A.

Pouche²⁰ states that bronchopneumonia is caused by pneumococci of the higher types. Pneumococcus antiserums have not controlled the disease to date as types of specific serum, until recently, has only been available for Types I, II and III.

The Treatment of Lobar Pneumonia with Rabbit Antipneumococcus Serum—E. H. Loughlin, R. H. Bennett and S. H. Spitz²¹ treated 69 patients with lobar pneumonia caused by pneumococci of Types I, II, V, VII, VIII and XIV, with homologous rabbit antipneumococcus serum. There were 5 fatal cases, 3 of Type I, and 2 of Type II, in all of which serum treatment was delayed until late in the course of the disease. No patients died when treated within the first 90 hours of the disease. The mortality rate for the entire series was 7.4 per cent.

Forty of the 69 patients were successfully treated with a single projected dose. As much as 500,000 units, included in a volume of 500 cc of unconcentrated and refined rabbit antipneumococcus serum, was given in 1 administration without any untoward effects. The serum, while being administered, gave the patient no more discomfort than an intravenous infusion of physiologic solution of sodium chloride.

Bacteriemia was controlled in most instances even when severe. The blood was rendered sterile when the entire projected dose had been given. Toxins were quickly neutralized, and, in cases of Type I and II pneumonia, a rapid development of tissue antibodies was obtained as demonstrated by a positive reaction of the skin to pneumococcus polysaccharide (specific soluble substance).

An immediate reduction of the toxemia was usually obtained when only part of the projected dose had been administered. The patient frequently feels

better after the first 20,000 to 40,000 units have run in. The toxemia invariably disappears after the entire projected dose has been administered. Then, the patient usually falls asleep, despite the fact that insomnia may have been a major complaint, and, frequently, the patient falls asleep during the administration of the serum.

Usually, there is a rapid temperature decline and reduction of the pulse and respiratory rate; frequently coincident with the administration of the serum but most often just prior to or together with the critical fall in temperature. Bradycardia is occasionally seen after the temperature falls to normal.

Rabbit serum can be used without danger in the treatment of adults who have a sensitivity to horse serum or suffer from asthma due to horse dander. Two patients who were sensitive to horse serum were given rabbit antipneumococcus serum without any untoward reactions. The fact is important when treating pneumonia in children, many of whom have previously received antitoxins made from horses. Rabbit antipneumococcus serum will not sensitize children to horse serum antitoxins, which may be necessary at later periods of life. None of the patients treated were found to be sensitive to rabbit serum.

The incidence of serum sickness was lower with rabbit serum than with horse serum. The figure was 43 per cent for rabbit serum, as compared with 67 per cent for horse serum. Fever alone, of from 1° to 3° F., occurred in 26 per cent of the patients who had serum sickness, urticaria in 60 per cent and arthritis in 14 per cent. There was no lymphadenitis in patients treated with rabbit serum. Serum sickness began between the seventh and the thirteenth day and lasted an average of 3½ days. Rabbit serum sickness occurred an average of 3 days later

than horse serum sickness. The febrile reaction, when it was the only manifestation of serum sickness, appeared from 3 to 4 days earlier than it did when it was accompanied by either urticaria or arthritis. Fever alone occasionally preceded either the urticaria or the arthritis and in 1 case continued for 12 days after the urticaria had disappeared. The arthritis and urticaria were milder than those seen in horse serum sickness. Circulatory collapse, which is noted occasionally with horse serum sickness, was not seen with rabbit serum sickness.

Chills following the administration of the rabbit serum occurred in 65 per cent of the cases. These chills began from 20 minutes to 1 hour after the administration of the serum was begun, usually after about 45 minutes. They were either mild or moderate and, other than the induction of warmth, did not need special treatment. At no time were they severe enough to be alarming. They were frequently followed by a rise in temperature. The individual peculiarities of the patients, and not the lot of serum used, affected the frequency of occurrence of the chills. Although several patients received the same lot, they did not all have chills. The rate of administration and the quantity of serum used did not seem to influence either the occurrence or the severity of these reactions. The administration of rabbit antipneumococcus serum was preceded in most instances by the giving of acetylsalicylic acid. Although this drug limited the rise in temperature incident to the chills to 1 or 2° F. and lessened the severity and duration of the chills, it did not decrease the frequency of occurrence. Chills did not recur with as great frequency after the second and third doses of serum when these were given. However, if they occurred after subsequent doses, they disappeared at the

same time as they had after the first dose but were usually milder.

Experiences with Serum Treatment of Croupous Pneumonia—W. T. Andersen²² found pneumococci of different types, most often Types I, VII, and III, in 41 of 60 patients with acute pulmonary diseases. Pneumococci were demonstrated in 30 of the 34 patients with croupous pneumonia, and 24 were treated with type specific rabbit serum. In the patients with Type III the effect was negative or doubtful; in the others good, with a few exceptions. The importance of an early start of the serotherapy was demonstrated. About 80 per cent of the patients had serum sickness about 10 days after the treatment, in 2 cases this contributed to the fatal outcome. There were only 2 deaths in the remaining 22 cases, both in cases considered hopeless at the start of treatment. Complications were rare. Treatment with type specific serum is a definite therapeutic advance, especially if the serum production is improved so that the grave serum conditions can be avoided, till then, extreme care is called for in treatment with serum of Type III.

Roentgen Therapy of Lobar Pneumonia—E. V. Powell²³ reports that in the last 4½ years, roentgen therapy was used in 104 cases of lobar pneumonia, including cases of infection due to Types I, II and III pneumococci and other bacteria. Only 5 of the patients have died, a mortality of just under 5 per cent.

The results in the treatment of Type I infections seem to have been better when roentgen therapy was used rather than serum. Because of the varying reports of its value, serum has been used in treating other than Type I pneumonias. Whatever the reason for the beneficial effect may be, wide experience has shown that roentgen therapy of carbuncles, furuncles and many other acute

infections is probably the method of choice. Roentgen therapy should be the preferred method in the treatment of pneumonias. So far the only contraindication seems to be definite leukopenia, such as is encountered occasionally in patients with postinfluenzal pneumonia.

A Further Evaluation of Artificial Pneumothorax in Lobar Pneumonia

—F. G. Blake²⁴ states that artificial pneumothorax seems to be of value for the relief of pleural pain in selected early cases of lobar pneumonia. It has not been shown to have any curative value in this disease.

Editor's Note: In view of the fact that pneumothorax treatment of pneumonia has been known to increase the incidence of empyema by as much as 300 per cent, it is to be hoped that this negative opinion by a leading early exponent of the procedure will write *finis* to the treatment of pneumonia by a method which offers so little promise.

TRACHEA

Tracheal Hemorrhages

V. Cordier and P. Mounier-Kuhn²⁵ reserve the term tracheal hemorrhages for repeated hemoptyses, the tracheal origin of which is verified by endoscopy and in a less distinct manner by indirect tracheostomy. Patients may request medical aid at the time of their first hemoptysis or because, although apparently in good health, they have had blood in the sputum for some time. Systematic bronchoscopy and clinical examination may suggest the possibility of a tracheal hemorrhage.

The hemoptyses differ, a mouthful of blood may be expelled after a sudden effort, but, in the majority of cases, the expulsive cough is absent. In this respect the condition differs from tuberculous

hemoptysis, in which the expulsive cough is rarely absent. The expectoration without effort (but with retrosternal tingling) impresses and reassures the patient; in drawing the physician's attention to this, he puts him on guard against an overhasty diagnosis of tuberculous hemoptysis. A definite diagnosis should never be made without a tracheoscopy, which may reveal:

1. Individualized lesions, such as malignant or benign tumors, or in exceptional cases, syphilitic or tuberculous lesions;

2. Autochthonous tracheal lesions, which are diffuse, indicating sanguineous dyscrasias (tracheal purpura, angitis of Osler, etc.);

3. A hemorrhagic tracheitis with fixed topography, probably in relation to a tuberculous adenomediastinitis. These tuberculous lesions are old but the hemorrhagic tracheitis, although it may make careful observation necessary, does not have to be treated like a developing tuberculous process.

Besides these cases, there exists still another form of tracheal hemorrhage for which no explanation has yet been found.

Treatment—The authors state that treatment is of little avail. Local application of *cocaine-epinephrine* or of *silver nitrate* have an ephemeral effect in most cases. Inhalation of antiseptic vapors or similar measures are ineffective. The employment of *coagulants* is beneficial. If a spirochetosis is present, *acetarsonsone* is often efficacious. The *cautery* gives temporary improvement in angiomatous tumefactions.

RELATION OF CARBON DIOXIDE TO ARTIFICIAL RESPIRATION

F. S. Johnson²⁶ points out that a modification (raising and lowering the

arms at the elbows alternately with prone pressure) of the Schafer prone pressure method has been proposed by Hederer. An evaluation of this method has indicated the possibility of increasing the pulmonary ventilation in the Schafer method by more than 40 per cent. The great sensitivity of the respiratory center to carbon dioxide is well attested by the fact that artificial respiration applied to the extent of lowering the alveolar carbon dioxide as little as 0.2 per cent below normal is sufficient to cause apnea.

On the other hand, when the alveolar carbon dioxide pressure is raised by only 2 mm., the breathing is increased about threefold. If the carbon dioxide of inspired air is increased to 4.5 per cent, it is impossible to produce an apneic pause, regardless of how forcefully the artificial respiration may be carried out.

Every form of manually applied artificial respiration should be accompanied by the inhalation of carbon dioxide whenever possible. The use of an apparatus of the type of the H-H inhalator is recommended in connection with artificial respiration.

FILTRABLE VIRUSES IN INFECTION OF THE UPPER RESPIRATORY TRACT

A. R. Dochez, K. C. Mills and Y. Kneeland, Jr.²⁷ state that it has been demonstrated by a large series of transmission experiments on human beings that there exists in the common cold a filtrable virus which in all probability is the primary etiologic agent and can interact with the various pathogenic agents of the upper respiratory tract to produce more severe infections. The evidence, however, from numerous bacteriologic observations during transmission experiments is to the effect that the uncomplicated cold in adults is practi-

cally a pure virus disease. Certain of the biologic properties of this virus have been investigated, and a method has been developed for its artificial cultivation and preservation.

INFLUENZA

Etiology—It was logical to apply the technic used in investigating colds to the problem of influenza. Influenza is a disease in the study of which one is faced at the outset with a difficulty of definition. In the first place, there is an obvious clinical difference between the severe manifestations of the 1918 pandemic and the milder manifestations seen in the small outbreaks of recent years. In the second place, it is difficult to make a satisfactory clinical diagnosis in an isolated case, with a resulting tendency for the physician to make a diagnosis of influenza in cases of sinusitis, streptococcal infection of the throat, gastroenteritis, and, in fact, any febrile disorder in which the cause is uncertain. The great volume of research during and immediately after 1918 concerned itself chiefly with the bacillus of Pfeiffer (*Haemophilus influenzae*), as well as with 1 or 2 other organisms, and an enormous mass of contradictory evidence and opinion was recorded. Experiments at that time designed to test for the presence of a filtrable virus of influenza were few in number, limited in scope and contradictory in outcome.

P. H. Long²⁸ reported transmission experiments on chimpanzees suggesting the presence of a filtrable virus in influenza. However, O. Costa Mandry, P. Morales Otero and J. Suarez²⁹ failed in an attempt to transmit influenza to human beings by means of filtered throat washings.

Studies of influenza were made with material derived from patients who had

the disease in 1931, 1932, 1933, 1934 and 1935, in the winter months, when mild influenza of the interpandemic variety was prevalent. Material was obtained from 1 patient in each of the 5 years mentioned. In the first year transmission to human volunteers was done with a filtered nasal washing directly after its being obtained from the patient; in the subsequent years, the material was cultivated in anaerobic tissue medium and tested after many transfers *in vitro*. A total of 39 tests on human volunteers was made under conditions of strict quarantine with the 5 materials mentioned. With 4 of these, a virus was demonstrated which, although productive of some constitutional reaction, could not be distinguished with certainty from the virus of the common cold. The fifth virus, obtained originally in a small but clinically severe outbreak, did produce in 1 of several volunteers an acute febrile disorder resembling influenza. From this limited number of experiments, it was possible to conclude that a filtrable virus had been recovered from patients with interpandemic influenza.

W. Smith, C. H. Andrewes and P. Laidlaw³⁰ in England reported the isolation of a filtrable virus from a patient with influenza which produced a febrile catarrhal disorder when introduced into the nasal passages of ferrets.

Several strains of the virus pathogenic for ferrets have been obtained, and they have been obtained exclusively from patients with typical attacks occurring in fairly severe outbreaks of the disease. Once established in ferrets, the disease can be transmitted to white mice, in which, after a few passages, it produces a fatal pneumonia. Protective substances against this virus are found in the serum of ferrets recovered from the disease and also in the serum of human convalescents, as well as in many normal human

serums. The production of antiviral substances in the serum can also be artificially effected by injecting virus into such unsusceptible animals as the rabbit and the horse. Immunologic studies performed with these various serums indicate that strains of influenza virus from different parts of the world are similar. The virus can be cultivated in fluid medium containing minced chick embryo tissue under aerobic conditions, and it has also been shown to propagate in the chorioallantoic membrane of the developing chick embryo.

Attempts to initiate a transmissible virus disease in ferrets with material derived from persons with common colds or from persons with any condition except typical influenza in fairly severe outbreaks have been failures.

To summarize, the primary etiologic agents of certain acute infections of the upper respiratory tract seem to be filtrable viruses; the fact that virus from patients with severe influenza is pathogenic for ferrets and can be cultivated best in aerobic medium, while virus from patients with colds or related infections is not pathogenic for ferrets and has been cultivated only under anaerobic conditions suggests that there exist at least 2 different types of filtrable virus—the cold virus and the virus of epidemic influenza.

A disease was established in mice by intranasal inoculation of cold virus growing in the chorioallantoic membrane of the chick embryo. This disease was characterized by areas of pulmonary consolidation and was fairly readily transmissible in series, although it did not carry so high a mortality rate as disease due to influenza virus in mice. Preliminary studies with immune serums were apparently showing an immunologic dissimilarity between cold virus and influenza virus when the course of

the experiments was interrupted by the appearance of a new and highly fatal virus which became mingled with all the strains of cold virus and abruptly terminated the experiments. This new virus was found later to be present occasionally in the lungs of apparently normal mice and to undergo a rapid enhancement of virulence on repeated intranasal passage, a fact which makes great caution necessary in interpreting results obtained with such a technic.

Treatment—A. R. Dochez, K. C. Mills and Y. Kneeland, Jr.,²⁷ were unsuccessful in developing active immunity against infection of the upper respiratory tract in human beings. The attempt was based on the successful vaccination of certain animals against virus infections such as canine distemper and especially swine influenza. The latter disease furnishes somewhat of an analogy to infection of the human upper respiratory tract as it results from the combined activity of a filtrable virus and a bacterium, *Haemophilus influenzae* suis, resembling the bacillus of Pfeiffer in man. Although this bacterium is necessary to produce the full clinical severity of the disease, it is powerless to initiate it and a solid active immunity can be generated in swine by parenteral injection of living virus alone.

Based on the assumption that the cold virus was similarly the agent of primary etiologic importance in human colds, an attempt was made to create an active immunity in man by the same method. Having developed a technic for the production and preservation of cold virus which rendered it available at all times and in a condition of proved bacteriologic sterility, it was used in this experiment.

After a preliminary trial with chimpanzees, which yielded encouraging evidences of active immunity, several

groups of human beings were given subcutaneous injections of living virus. Careful study of their subsequent clinical histories failed to reveal any real evidence that protection against colds had been developed by this means. The explanation of this negative result cannot yet be made. It may be due to the existence of a multiplicity of strains of virus, to the impossibility of preparing virus in large quantities free from the constituents of the nutrient medium or to the possibility that resistance to colds is a purely local rather than a general bodily phenomenon.

With regard to the prophylaxis of *influenza*, the situation may be regarded as more encouraging. Immune substances have been reported in the serum of persons vaccinated with a mouse passage strain of influenza virus cultivated in tissue medium, and active immunity in a group of persons similarly treated has been reported.

Light has been shed on complex mechanisms and methods have been developed which may have future value.

BRONCHI

Lipiodol Bronchography

Diagnosis—L. W. Burge and J. W. Post³¹ report that, in 1918, Chevalier Jackson used bismuth and barium powders as a roentgenologic contrast media. In 1920, H. L. Lynah used a mixture of bismuth and pure oil. In 1922, J. A. Sicard reported using lipiodol.

Lipiodol, a poppy seed oil containing 40 per cent iodine, is opaque to x-ray and is an effective roentgenologic contrast media. The iodine is so combined with the oil that in the bronchial tree the iodine is liberated so slowly it is nonirritating.

It is of use in the following instances

1. To determine the source of coughed-up purulent nontuberculous sputum;

2. To determine the point of blockage in the various types of atelectasis;

3. To determine the open or closed condition of abscesses or tuberculous cavities;

4. To demonstrate the amount of constriction and the location of the constriction in bronchial stenosis and spasm, such as asthma.

To apply the lipiodol, the patient's throat is sprayed with a 10 per cent cocaine solution while the tongue is held far forward, so that no cocaine enters the esophagus. Cocaine, even in a 10 per cent solution, is not absorbed from the bronchial tree or pharynx sufficiently to give symptoms. After cocainization, and with the tongue held in the same position, lipiodol is applied to the bronchial tree by dropping it on the base of the tongue during respiration.

It is advisable to x-ray the patient immediately following the instillation of the lipiodol, before he coughs. Routine anteroposterior and lateral roentgenograms are made. The lateral bronchogram is of value because this projection helps to separate the overlapping shadows of the bronchial tree that result from the anatomical overlap of the lobes of the lung.

As bronchography is a contrast study, it is preferable to sacrifice the finer lung markings for blacks and whites.

In the trachea and larger bronchi, there will be developed a normal and abnormal mucosal pattern.

There are 3 types, or 3 stages, of the same bronchiectatic lesions:

1. **Tubular**—The outline of the bronchial arborisations show a nodular outline instead of the normal smooth appearance, with increase in bronchial diameter.

2. **Fusiform**—The typical clubbed finger picture is observed. Depending upon the stage, the contrast material may or may not enter the alveoli. If there is a distinct filling defect, localized bronchiectatic atelectasis is indicated.

3. **Saccular**—There occurs the rounded grape-like outlines of lipiodol, either completely filled or showing a fluid level.

Bronchography is a very valuable adjunct in the diagnosis of bronchiectasis, for by no other means can it be definitely diagnosed, particularly early enough for therapy to be of any real value. The contrast study permits the serial study of the progress of the patient.

Many times there is displacement of right and left main stem branches. Invariably, this finding is the result of collapse of a lobe with emphysematous distention of the superimposed or underlying lobe. The resulting x-ray pictures of the bronchus resemble a steerhorn.

In some cases the tuberculous cavities fill readily, and bronchography is of value in differentiating cavities, localized pneumothoraces and pleural blebs or rings.

By reason of dependency, the bases are more liable to bronchiectatic lesions than elsewhere, and the right side more than the left. The upper branches of the bronchial tree are not immune.

Treatment—*Lipiodol* is useful in the treatment of the following conditions:

1. All forms of asthma.
2. Bronchiectasis;
3. Chronic retentive bronchitis.

The iodine content adds weight to the oil and gravity carries the oil to the bottom of the cavity or bronchus and mechanically floats any contained pus or secretion to a level where it can be coughed up.

Irrespective of the cause or duration of asthma, the instillation of lipiodol into

the bronchial tree is promptly followed by the expectoration of opaque pus, with a relaxation of the spasm. The frequency of treatments necessary to maintain improvement varies in different cases, but taking into consideration that mild hay fever often causes the severest asthma and *vice versa*, one is led to suspect that the asthma in any case is dependent to some extent upon the emptying ability of the bronchial tree in the individual case and upon imprisonment of purulent secretion below the point of bronchiolar constriction.

F. W. Burge and J. W. Post³¹ state that the time of excretion of lipiodol is a moot question. In some cases the lungs are clear in 24 hours and in others the lipiodol may remain for months. The cough impulse is a consideration.

D. H. Ballou and H. C. Ballou³² claim that the oil is eliminated more quickly from diseased than healthy areas in some cases.

BRONCHIECTASIS

Etiology — New Conception of Bronchiectasis: Preliminary Report

--S. H. Watson and C. S. Kibler³³ point out that bronchiectasis is seldom found without at least some evidence of sinusitis. Many cases of bronchiectasis have some manifestation of allergy (hay fever, asthma, urticaria, eczema or rhinitis).

Frequently and in practically all cases of bronchiectasis there is a high percentage of eosinophils both in the nasal secretions and in the sputum. This gives the impression that bronchiectasis has an allergic background.

Cutaneous tests and case histories confirm the hypothesis that sinusitis and bronchiectasis in a patient have a common etiology, allergy. Also, many cases of bronchiectasis respond to elimination of allergens or to desensitization treat-

ment with offending substances and show marked reduction of cough and sputum, or even entire elimination of symptoms if the case is not too far advanced.

The following is a new etiologic classification of bronchiectasis:

1. Congenital, similar to congenital cystic disease of the lung;

2. Mechanical, due to pulmonary fibrosis, particularly associated with fibrous pleuritis;

3. Allergic, the result of hypersensitivity.

Of the 3 types, the allergic is by far the most important, comprising about 90 per cent of the cases coming to the physicians' attention.

Allergic bronchitis predisposes to bronchiectasis because swelling of bronchial mucosa and exudation of tenacious secretion interfere with efficient pulmonary drainage and, favored by coughing, the chronic infection which results gradually weakens the wall of the bronchial tree. Bronchiectasis usually occurs in the most dependent portion of the lung, the posterior half. This location is the most unfavorable point of drainage.

Physical and Psychological Manifestations — E. D. Churchill³⁴ states that a productive cough with profuse foul sputum is usually the presenting symptom in bronchiectasis, causing distress and inconvenience to the patient, and almost invariably rendering him sensitive to its effect on others. He becomes reluctant to appear anywhere at social gatherings. Laughter may induce a spell of coughing, the time of "emptying" is difficult to calculate accurately, and the patient is frequently acutely embarrassed. The result is a sensitive individual who shuns social contacts and becomes increasingly shy and solitary.

In bronchiectasis, there are acute pneumonic episodes initiated by respira-

tory infection. Between acute attacks, the smoldering infection in the lung gives rise to a sense of fatigue that is insidious and vicious in its effects. This lack of physical endurance paralyzes plans and ambitions for a future career. If the symptoms are at all severe, the patient early becomes aware of the impossibility of getting married. The menstrual cycle is frequently disturbed by the chronic invalidism, and young women with this disease usually consider themselves unfit to bear children.

E. D. Churchill³⁴ states that an established bronchiectasis is not a self-limited disease, but a persistent and often progressive malady, constituting even in its milder forms a serious physical and psychological handicap to the patient and eventually terminating in death.

Treatment—E. D. Churchill³⁴ performed *lobectomy* on 84 cases of bronchiectasis with a mortality rate of 47 per cent. All of the patients who survived were greatly helped and about 85 per cent were completely cured.

If bronchiectasis is recognized and treated early in life, serious psychological difficulties and personality changes may be avoided. Patients between the ages of 5 and 12 years stand lobectomy well. Young adults should be operated upon before they assume the social responsibilities of marriage, or before the door to a happy marriage is closed to them by their illness.

Conservative remedies and operations may, in some instances, result in gratifying symptomatic relief, but there is no real cure for bronchiectasis but *extirpation of the diseased segment* of lung.

BRONCHOPNEUMONIA

Bacteriologic Etiology of Bronchopneumonia in Infants—A. Pouche²⁰ cultured pharyngotracheal se-

cretions of 60 infants suffering from primary bronchopneumonia. Cultures were also done with material taken from the lung or the pleural cavity by puncture, either during life or immediately after death. Hemocultures were also made. Several bacteria, especially pneumococci of the Type IV and hemolytic streptococci were identified.

Cultures with the pharyngotracheal secretion are of scanty diagnostic etiologic value. Noncausal bacteria frequently appear in the cultures. Hemocultures also are of scanty diagnostic value. Cultures from lung or pleural material showed pneumococci of Type IV and hemolytic streptococci in all but 1 case. The former was predominant in the cases which evolved to recovery whereas the latter was predominant in the cases which ended in death of the patient.

Disagreement in the literature as to the etiology of primary bronchopneumonia in infants depends on the various methods used in the bacteriologic researches. The disease is caused by pneumococci of Type IV. Pneumococcus antisera have not been effective because of the fact that up till now they have been prepared with pneumococci of Types I, II, and III, which are not the etiologic agents.

LUNG ABSCESS

Etiology—W. P. Warner³⁵ reviewed 98 cases of lung abscess in the Toronto General Hospital during the years 1926 to 1936, inclusive. Cases in which the abscess was tuberculous or part of a general pyemia were excluded. The unsatisfactory results of the various forms of treatment emphasize the importance of prophylaxis.

Many abscesses of the lungs could be prevented if the technique of anesthesia

used in certain operations on the upper part of the respiratory tract was changed. Better oral hygiene would also eliminate a fairly large number of cases. Blood-borne infection, either with or without large emboli, is an obvious cause of some abscesses. Abscesses of the lung occurring secondary to the extraction of teeth could be completely or almost completely eliminated if teeth were extracted under local anesthesia, or if only a few teeth were removed under general anesthesia, and care taken to prevent the aspiration of foreign matter into the lungs.

Analysis of Causes of Death in 100 Consecutive Fatal Cases—J. D. Rives, R. C. Major and S. A. Romano³⁶ determined the causes of death in 100 consecutive fatal cases of nontuberculous abscess of the lung, exclusive of any due to tumors, foreign bodies or bronchiectasis. The duration of the disease before treatment, the extent and severity of the infection and the methods of treatment employed were not the primary contributing causes of death. Three more or less controllable factors contribute to the mortality. They are spreading pneumonitis, empyema and anemia. Anemia may be readily controlled by transfusion and by adequate supportive treatment. Empyema may be avoided in most instances if surgical treatment is instituted early in superficial lesions and if needling of the chest is abandoned. Spreading pneumonitis, the chief cause of death, may be minimized if the following are avoided: attempts to drain the abscessed cavity during the acute stage, compression therapy, especially when the cavity is incompletely drained; all measures, such as intermittent postural drainage, likely to cause severe paroxysms of coughing while the cavity is full, and surgical drainage in the acute stage and at any time in deep-seated abscesses. Approxi-

mately half of the deaths were probably not preventable, but in many of the remaining fatal cases the fatality might have been avoided by adequate supportive treatment combined with the judicious use of commonplace methods of bronchial or external surgical drainage. Spreading pneumonitis was the cause of death in four-fifths of the fatal cases.

Treatment—The best results will be attained by an orderly plan of treatment which utilizes supportive measures, bronchial drainage and surgical drainage according to their proper indications, and which is continued until the abscess has disappeared completely.

New Simplified Technic for Drainage of Lung Abscess Employing Graduated Trocars—() H. Wangenstein³⁷ states there is danger in draining a pulmonary abscess in the manner in which a soft tissue abscess is evacuated. The difficulty with the cautery or surgical diathermy method is that more lung tissue is destroyed than is necessary.

A series of *graduated trocars* with a knife-like edge, aided with the *coagulation current* of the surgical diathermy apparatus, serves the purpose simply and satisfactorily. The track of the aspirating needle into the abscess cavity can be followed by passing increasingly larger trocars over one another, applying the coagulating current in turn to each, until a sufficiently large tunnel has been established to permit adequate drainage.

With this method bloodless drainage of a pulmonary abscess, with minimal destruction of lung tissue, may be done quickly.

Pneumothorax in Pulmonary Abscess—K. Kollmeier³⁸ says that *pneumothorax therapy* is advised by few owing to the dangers of this method. Pneumothorax therapy in pulmonary abscess readily leads to an involvement

of the pleura and to empyema. Pneumothorax therapy of pulmonary abscess was used as early as 1833, long before pneumothorax was introduced into the treatment of pulmonary tuberculosis. Pneumothorax therapy was used in 7 of 10 cases of pulmonary abscess. In all except 1 of the cases, the abscess was either in a central location or near the hilus. This localization of the abscesses was chiefly responsible for the especially favorable action of the pneumothorax therapy. Involvement of the pleura was observed in none of the cases. After the pneumothorax was induced there was an improvement in the general condition, and in some cases the cough and expectoration disappeared. Moreover, the fever usually decreased and the appetite improved.

Only small quantities of air should be introduced. The pressure should remain negative, as no great pressure should be exerted on the lung. Refilling should be continued until the fever has subsided and cough and expectoration have disappeared.

Pneumothorax is indicated in abscesses with a central or juxtahilar location, but in juxtapleural abscesses it should be used with the greatest caution or not at all.

ATELECTASIS

Etiology—"Plate-Like" Atelectasis of the Lung—A. Ettinger³⁹ reports that small areas of pure atelectasis without complicating secondary changes in the parenchyma are represented in the roentgenogram by "plate-like" shadows in the lung, which appear as horizontal stripes in both posteroanterior and lateral views. Previously such horizontal stripes frequently have been mistaken for fibrinous deposits on the pleura. These stripes

have been observed in association with 3 groups of conditions:

1. Abdominal diseases.
2. After contusions of the chest.
3. Minor upper respiratory infections.

By autopsy controls it was demonstrated that these plate-like shadows were due to small atelectatic areas.

These shadows developed during the re-expansion of a lobar infectious atelectasis in a number of children with typical acute lobar collapse due to upper respiratory infection. The horizontal stripes appeared in the roentgen ray film during the stage of reinflation. They represented at this time the only abnormal finding. Clinically, the health of the patient seemed to be fully restored.

Massive Atelectasis Following Cyclopropane Anesthesia—O. R. Jones and G. E. Burford⁴⁰ report that in 4 deaths which occurred following the use of cyclopropane as an anesthetic, autopsy of these cases showed massive collapse of 1 or both lungs. Also pulmonary complications following long-continued cyclopropane anesthesia, especially for operations on the stomach, have increased more than should be expected. They report that complete atelectasis of a whole lobe has of recent years been assumed to be obstruction in the main bronchus followed by absorption of the alveolar gases behind the obstruction. When the obstruction has become effective, the time required for the development of atelectasis depends on the rate of absorption by the lung of the gases distal to the obstruction, provided the circulation in the lung is intact and the alveolar epithelium undamaged. Great variations occur in the rate of this absorption. Anesthetic gases are absorbed in a matter of minutes, as are also oxygen and carbon dioxide. The inert gases, helium, hydrogen, and nitrogen, require from 18 to 26 hours for absorption.

The normal lung filled with air contains about 79 per cent of an inert gas, nitrogen, which has a supporting effect upon the expanded alveoli.

When during an operation the rapidly absorbable gases fill the alveoli this support is quickly lost as the gases are absorbed and the alveoli collapse because of the lack of inert gas which should be present to keep them distended. This condition favors atelectasis of the lungs.

Collapse of the lungs occurred in 4 fatal cases, and in 3 instances occurred only some minutes after the anesthetic had been discontinued and the operation finished. In no case was an obstructing plug found at autopsy in any of the main bronchi.

Diagnosis—"Plate-Like" Atelectasis of the Lung.—A. Ettinger³⁹ reports a case of acute lobar collapse due to upper respiratory infection in which, in the end stage of re-expansion, thin horizontal shadow stripes were seen in the area previously collapsed, and were interpreted as "plate-like" minute areas of atelectasis which were caused by the occlusion of small sized bronchi.

In the differential diagnosis, pleural adhesions alone have to be considered. The appearance of the atelectatic area as thin stripes in both the anterior and lateral films makes it obvious that we are dealing with a plate-like and not with a linear structure. The intrapulmonary origin is therefore evident.

Fleishner explains the appearance of these plate-like shadows by a mechanism which he calls "directed collapse." While in pneumothorax the lung can retract from the lateral chest wall, because of the change of pressure within the chest cavity, conditions for collapse in obstructive atelectasis are fundamentally different. In this condition the lung cannot retract from the chest wall. Even if no pleural adhesions are present, the nega-

tive pressure acts as an adherent force between the surface of the lung and the chest wall and prevents the collapse of the lung toward the hilus. As there is no possibility for the lung to shrink in a costomediastinal direction, as in pneumothorax, the tendency of the atelectatic area to diminish in extent can take place only in a craniocaudal direction, perpendicular to the axis of shrinkage in pneumothorax.

Lipiodol Bronchography.—F. W. Burge and J. W. Post³¹ state that lipiodol bronchography is of value to determine the point of blockage in the various types of atelectasis.

Prophylactic Treatment—Massive Atelectasis Following Cyclopropane Anesthesia.—O. R. Jones and G. E. Burford⁴⁰ believe that to prevent atelectasis following cyclopropane anesthesia, an inert gas of 1 type or another should be added to the cyclopropane mixture. Nitrogen would be effective, but the most useful is either hydrogen or helium.

Re-expansion in Atelectasis.—G. H. Jennings⁴¹ cites a case that developed an atelectasis of the lower left lobe in the course of an attack of acute bronchitis with small areas of bronchopneumonia. This was due to plugging of the bronchioles in that lobe with secretion during the time when movements of the left lung were restricted owing to pleuritic pain. When sputum was coughed up later, the lobe re-expanded. Respiratory exercises assisted in this process. The lobe was collapsed for about a month. A cylindric dilatation of the bronchi had developed within the collapsed lobe. With re-expansion of the lobe the bronchi become of normal width.

This case illustrates the possibility of bronchial dilatation in atelectatic lobes disappearing if the lobe re-expands. Methods for promoting early re-expansion of atelectatic lobes should be em-

ployed. Among these, postural and bronchoscopic drainage, inhalation of barbon dioxide and respiratory exercises have all been used with success. Lobectomy should not be considered until such methods have been tried and the permanence of the atelectasis proven

CYSTS OF LUNGS

Differential Diagnosis—D. L. Anderson⁴² states that in diagnosing a cystic disease of the lung many difficulties are encountered. A history of dyspnea, varying degrees of cyanosis, wheezing or cough at birth or during early childhood in the absence of an acute infectious process or a history of an aspirated foreign body is suspicious of a "tension" cyst. The history pictured is often one of spontaneous pneumothorax.

The most frequent chief complaint occurring in 67 cases reviewed was dyspnea. The symptom may make its appearance at birth or late in life, suddenly or insidiously, constantly or intermittently. As shown in the following chart 18 cases (26.8 per cent) had shortness of breath as a chief complaint, while 10 cases (14.9 per cent) claimed dyspnea and cyanosis as the first difficulty. More than 68 per cent stated that they experienced air hunger at some time during their illness.

CHART OF CHIEF COMPLAINTS

Complaint	Cases	Percentage
Dyspnea	18	26.8
Dyspnea and Cyanosis	10	14.9
Cough and Expectoration	12	17.9
Hemorrhage	8	11.9
Pain	4	5.9

Dyspnea may be attributed to 1 or more causes. First, the solitary cyst may reach such an enormous size or, if of the multiple variety, may occupy such

a large pulmonary area as to cause a paucity of lung tissue. Second, the cyst may encroach upon adjacent structures leading to atelectasis, kinking of the large bronchi, angulation of the trachea, displacement of the mediastinal contents and elevation of the intravenous pressure.

Rupturing of a cyst or cysts, if located peripherally, often accounts for spontaneous pneumothorax. The most frequently mistaken diagnosis for cystic disease is spontaneous pneumothorax.

Inflammatory conditions such as pneumonitis and influenza associated with cystic disease will lead to dyspnea in a very large percentage of cases.

Twelve cases (17.9 per cent) had cough and expectoration as the outstanding symptoms. As a rule, the cough is productive and frequently offensive, especially in the long-standing infected multiple type. There is seldom gross expectoration in the balloon cyst of childhood.

Hemorrhage may occur in the single cyst type of adults but rarely in the balloon cyst. Eight cases (11.9 per cent) of the series had pulmonary hemorrhage as the chief complaint, and 13 patients reported "blood spitting" at some time during their illness. The hemorrhages were usually moderate in quantity.

Pain in the chest occurred less frequently than any other symptom, only 4 cases (5.9 per cent) giving pain as a chief complaint.

A very large percentage, 16.9, gave no history suggesting lung cysts and the finding of the condition was purely accidental.

In other cases, signs of spontaneous pneumothorax, cavity formation, emphysema, consolidation, and fluid formation were found in the same patient.

With the absence of a family history of tuberculosis, a negative sputum, negative intradermal tuberculin test, the ab-

sence of foreign body aspiration, and in their place a history of intermittent dyspnea, cyanosis, and cough over a period of time, a lung cyst should be suspected.

Treatment—V. S. Randolph⁴³ states that chronic empyema occurs when the lung has not been fully re-expanded during drainage of the acute empyema, and should be avoided by proper *drainage* of acute empyemas and re-expansion of the underlying lung.

Clear fluid of acute empyema should be *aspirated*. When the fluid ceases to be clear, *closed drainage* should be instituted at the lowest point in the pleural cavity. A tube large enough so that it will not plug easily must be used to insure continuous drainage. *Irrigation* is of some value. Chronic empyema may be cured by "*unroofing*" with or without some form of *thoracoplasty*.

FUNGUS DISEASES OF LUNGS

Pulmonary Manifestations of Coccidioidal Granuloma

Etiology—F. P. Miller⁴⁴ states that the causative organism is the coccidioides immitis, which is an irregular protoplasmic body with a double contoured, highly refractive surrounding membrane or capsule. They multiply by sporulation.

Most cases of coccidioidal granuloma reported give a history of having spent a period of time in the San Joaquin Valley in California. However, a sizeable number of cases have been reported of persons who had never been in California.

The fungi enters the body either through an abrasion or by inhalation of dust and acts upon the host in producing a lesion of either an acute or chronic manifestation, depending upon the virulence of the invader. There is no history of human case to case infection.

The following 2 cases were employed upon the same project, each less than 3 months and approximately ½ mile apart, and each was exposed to dusty atmosphere.

Case No. 1, on 9/28/34, accidentally scratched his hand between the third and fourth metacarpal bones, while employed on an irrigation project in the vicinity of La Mesa, California. His particular work was tamping the dirt in and around the large flume pipes and he was exposed to considerable dust. During the course of his work, he would occasionally accidentally tear off the superficial crust of the skin abrasion.

Case No. 2 gave a history of employment for 2 years by a number of construction companies and the greater part of this employment was in San Diego County.

Pathology—Case No. 1, at post mortem, showed a healed abrasion 2 mm. in diameter on the back of the right hand between the third and fourth metacarpals above the base of the finger. The brain appeared edematous and the parachnoid was markedly congested.

The lungs had a lobar pneumonia in the stage of red hepatization, and there were many small caseous cavities, surrounded by dense fibrotic scar tissue, suggesting tuberculous origin.

Microscopic findings were as follows. Surrounding the necrotic area there was fibrosis, dense in some places, indicating that the process had been present for considerable period, and farther removed from the necrotic area, there was an increase in fibrosis with obliteration of the lung alveoli. A few typical spheroidal organisms were found within the giant cells.

Case No. 2 was seen after an operation. At this time, he had numerous papular and papulopustular skin lesions. The latter lesions had a papular base

with a pustular apex. These were approximately 1 cm in diameter with elevated edges and a depression in the center. These were indiscriminately located over the body.

There was a moderate cervical adenopathy, particularly upon the right side. The chest revealed an enlarged hilus with retrogressive changes in the right lung indicative of recent pathology, and in the left there was a pneumonia with a great deal of thickening at the left base.

In this case, the post mortem findings were of red and gray hepatization. No cavitation was present.

Microscopically, the picture presented was predominantly epithelioid tubercle formation, and there was quite a central caseation necrosis in a few of these.

In a third case of coccidioidal granuloma, the visceral pleurae was sanded by fine miliary lesions, which often can be felt easier than seen. There was a large, firm caseous enlargement of the lymph nodes immediately above the tracheal bifurcation, a total mass almost as large as a golf ball. This structure on section shows almost total replacement of lymphoid tissue by a mixed caseous and purulent granuloma formation in and around the nodes with a rather slight peripheral fibrosis. Granuloma nodules of walnut size were found near each apex, adherent to both visceral and parietal pleurae, a somewhat larger nodule at the right base, and 3 or 4 scattered smaller nodules throughout the lung. All showed mucopurulent centers with a granuloma-like wall and the gross appearance to be closer to that of a lung abscess than one of a tuberculous origin. The bronchi were filled with stringy mucopus and the entire bronchial tree was thickened and semibronchiectatic.

Symptoms—Case No. 1 complained of a constricted sensation in his chest,

associated with fatigue, night sweats and inertia.

Case No. 2 became ill with a great deal of epigastric distress, and excruciating pain throughout the upper quadrant. Cholecystitis was suspected and he was operated, but his gall bladder was negative. Coincident with this, he complained of chest pains of an indefinite character and had profuse night sweats.

Clinical Course—The primary pulmonary focus may remain dormant in the lungs for many years before becoming active. The duration of cases have been from 9¼ months to 62 months.

Case No. 1 had no symptoms until 3 weeks after injuring his hand, then a week later he was unable to open his jaw, had a markedly high temperature, and some rigidity in the neck musculature and was so gravely ill he was hospitalized, and died 3 days later.

A week after Case No. 2 developed symptoms, his chest films showed only an enlarged hilus. Films taken 6 days later showed pneumonic areas in the upper left. Films taken 5 days after this, showed the right lung clear with an extension of the pneumonia to the left base, and films taken again 5 days later showed a generalized pneumonia involving all lobes of both lungs.

Complications—In Case No. 2, the pulmonary lesions suggested a primary involvement of the tracheal and bronchial nodes, lymphatic spread along the bronchial tree with subsequent development of the dozen or so nodular lesions scattered through both lungs, and then a final miliary explosion through the lungs, liver, spleen and kidney.

In Case No. 2, there was parenchymal involvement and general filtration into the kidneys, liver, and spleen, with very little protective response on the part of the host, as fibrosis was apparently

lacking and the spheroid organisms were present in many tissues of the body.

Differential Diagnosis—Pulmonary coccidioidal granuloma is often confused with miliary bronchopneumonia or bronchiolitis, miliary tuberculosis (acute or chronic), miliary carcinomatosis, and second stage silicosis.

Diagnosis—Undoubtedly, Case No. 1 died from a terminal pneumonia and meningitis, although no coccidiodes were found in the meninges. The injury to the hand was irrelevant.

Roentgen Diagnosis—Due to the thick tenacious mucus which is present in some of these cases, there is a very shifting picture through the x-rays. There is a rapid migrating type of pneumonia, which may show evidences of clearing in 1 lung with an extension in the other. Also, there may be localized areas of atelectasis which may approach a more or less massive collapse

Pulmonary Moniliasis: Report of Fatal Case

Etiology—A. H. Davis and F. I. Warren¹⁵ reported a fatal case of pulmonary moniliasis due to *Monilia albicans*. The strain isolated from the sputum of the patient was subjected to different environments and the reactions on nutrient broths, each containing 1 per cent mannose, maltose, dextrin, lactose, dextrose, galactose, mannite, saccharose, levulose, dulcitate, rhamnose, arabinose and xylose were determined. The reaction of this strain of *Monilia* was constant on all the sugars. *Monilia* was found to be pathogenic for rabbits when injected intravenously and for white mice when injected subcutaneously or intraperitoneally but was not pathogenic for guinea pigs when 1 cc. of sputum containing the organisms was injected intraperitoneally.

Diagnosis—W. A. Dearman¹⁶ points out that at least 6 cases of primary pulmonary moniliasis have been observed on the Mississippi coast in the past few years. Identification presented considerable diagnostic difficulty. The acute cases of the disease resembled acute bronchopneumonia in onset, physical signs and clinical course, while the chronic types simulated advanced pulmonary tuberculosis. A diagnosis of *Monilia* infections can be made only by repeated examinations of the sputum showing an absence of tubercle bacilli. The diagnosis of pulmonary moniliasis should be considered in any case of pulmonary disease in which the etiology is questionable.

PNEUMONOCONIOSIS

Etiology—*Chronic Lung Changes in Electric Arc Welders*—N. Enzer and O. A. Sander¹⁷ observed 26 electric welders of low carbon steel with rods of the same composition for 3 years.

Chest roentgenograms in 5 of these, showed nodular shadows simulating a modified type of silicosis. In 5 others the trunk shadows were markedly exaggerated, the appearance simulating a pre-nodular fibrosis of the type seen in older foundry welders. The past occupational histories were checked in detail for exposure to silica dust, but the majority had welded in this plant since they began work, an average total of 19 years. These men were not breathing particulate matter to any appreciable degree other than that in the welding fume itself. Several of the 16 men in whom there was no x-ray appearance of nodulation had worked as welders in the plant even longer than those who showed definite nodulation. Each of the

5 men with nodulation had done more work inside of tanks than had the 5 showing only exaggerated trunk shadows but the latter 5 had welded inside the tanks considerably more than had any of the 16 men with perfectly clear lungs.

Deposition of iron oxide in the lungs was responsible for the x-ray appearance of nodulation. Functional impairment of the lungs with such iron deposits appears to be lacking, both as to the development of clinical symptoms or susceptibility to complicating infections.

Lung Findings in Foundry Workers—A 4-Year Survey—O. A. Sander⁴⁸ investigated some 4000 foundry employees, not only for changes in the lungs but for general physical changes as well. With half of the total group having had less than 10 years of exposure in the foundry, definite silicosis was found in about 7 per cent. Of the 279 persons with silicosis, 60 (22 per cent) had tuberculosis which either was definitely active or in which the activity was indeterminate. In 8 cases the tuberculosis was definitely active. Serial observations have suggested that silico-tuberculosis as seen in foundry workers is primarily a reactivation of a previously acquired but walled-off tuberculosis. Simple silicosis as seen in foundry workers is only slowly progressive, so much so that no visible changes have appeared in 4 years of observation. Moreover, the simple silicosis among these workers is only rarely sufficiently advanced to cause symptoms and incapacity for work.

The tuberculosis rate, among foundry workers at least, is not raised by exposure to dust in itself but rises only after silicosis becomes definitely established.

Diagnosis—H. I. Spector⁴⁹ states that a diagnosis of silicosis should be based upon:

1. History.
 - (a) Prolonged exposure to a dusty atmosphere containing a high concentration of silica, the individual particles of which are less than 10 microns in diameter;
 - (b) Symptoms such as dyspnea, dry cough, and pain in the chest;
 - (c) Lack of toxic symptoms.
2. Physical examination of the patient.
3. Fluoroscopic and roentgenographic examinations of the chest.
4. Macroscopic and microscopic examinations of the lungs.
5. Chemical examination of dried lung tissue for determining the amount of silica.

There is no pathognomonic symptom, sign, or x-ray shadow in silicosis that cannot be simulated by other diseases. Therefore, all factors must be considered in making a diagnosis of silicosis. The committee appointed by the American Public Health Association for the purpose of studying the roentgenological appearances in silicosis and the underlying pathological lesions makes the following statement in its report: "Only the physician who has examined the subject, has obtained an occupational history of any adequate exposure to silica dust, and has before him a suitable roentgenogram of the chest, should make the diagnosis of silicosis. The roentgenologist not in possession of these facts can merely state whether the shadows which he sees in a film are consistent with his diagnosis."

Prophylactic Treatment — Lung Findings in Foundry Workers—A 4-Year Survey—O. A. Sander⁴⁸ believes that control of the foundry hazard is best accomplished by eliminating at its source the dust generated by sand-blasting, sand chipping, sand grinding and shake-out operations. Combined with this, pre-employment examination and periodic examinations are essential,

POSTOPERATIVE PULMONARY COMPLICATIONS

Treatment With Intratracheal Suction—C. Haight⁵⁰ states that the stasis of secretions within the tracheobronchial tree is an important cause of postoperative pulmonary complications, such as atelectasis, aspiration "pneumonia," suppurative pneumonitis, and pulmonary abscess.

Constant maintenance of adequate intrabronchial drainage is essential for the prevention and treatment of such complications. Free drainage can be maintained by postural methods, by hyperventilation with 15 per cent carbon dioxide inhalations, by the administration of sufficient narcotics to control pain and promote effective coughing, and by well-directed nursing that will assist the patient in coughing.

Occasionally, intratracheal suction, by bronchoscopic aspiration or by intratracheal catheterization, must be used as an emergency measure when patients are literally drowning in their own secretions. Intratracheal suction is indicated when, despite the prophylactic measures mentioned, the cough remains wet and unproductive. In an unconscious patient, the presence of rhonchi, wheezes, or a wet type of breathing and cyanosis is suggestive of retained secretions.

Of the 2 methods of intratracheal suction, **bronchoscopy** is preferred when a single aspiration only is necessary and in definite cases of atelectasis. When repeated aspirations are necessary or when bronchoscopy seems too formidable a procedure, a soft rubber **Robinson-type** of **French catheter** No. 16 is introduced through the external nares, and when the patient coughs because of irritation of the larynx, the catheter is inserted into the trachea and aspiration

is applied. This procedure is carried out with the patient in the Trendelenburg position. The patient is turned from side to side during aspiration in order that the primary bronchi may be reached. The aspiration is usually continued for 1 or 2 minutes or until no further purulent material can be obtained. As suction tends to provoke excessive coughing and slight cyanosis, it is usually necessary to apply the suction intermittently by repeatedly pinching the catheter for a period of several respiratory phases from time to time, so that the patient will not be too much upset by the procedure.

The secretions tend to reaccumulate after a time and the aspiration may be repeated again in from 4 to 6 hours until the patient is able voluntarily to cough and expectorate effectively.

In 1 case, after a secondary closure of an abdominal wound following a gastric resection for carcinoma, the wound ruptured on the tenth postoperative day. Sudden marked cyanosis, dyspnea, coma, and loud râles, which developed 24 hours later, were not relieved by the use of an oxygen tent. Intratracheal suction was applied and the patient returned to consciousness 15 minutes later. Repeated suction was applied every 2 hours for the next day and every 4 hours for the next 2 days. X-ray examination revealed an extensive pneumonitis. From 10 to 30 cc. of purulent secretion were obtained at each aspiration. The cough became effective on the third postoperative day and intratracheal suction was discontinued. X-ray examination on the eighth day showed marked clearing of the pneumonitis, and the patient progressed to complete recovery.

The incidence and severity of postoperative pulmonary complications can be greatly decreased by adhering to such preventive and therapeutic measures.

SUPPURATIVE LUNG CONDITIONS

Postural Drainage—P. M. Holmes⁵¹ believes that postural or gravity drainage, an old and simple treatment, is effective in evacuating thick, heavy secretions if used correctly and long enough to suppurative conditions such as lung abscess, bronchiectasis, tuberculosis, and empyema with bronchopleural fistula, and should be tried before more drastic treatment is instituted.

To be effective, it is necessary that there be free drainage from the lesion into a main bronchus, and the treatment is more successful in those lesions located in the lower two-thirds of the lungs. Abscess and bronchiectasis of the apices are intractable with this method.

The *technic* consists in having the patient placed in a position that will permit drainage of the affected area by gravity. If the lesion is located at the base, the patient is instructed to hang over the edge of the bed for 5 minutes several times during the day, with the thorax as nearly perpendicular as possible. Each day, the time is increased by several minutes, according to the individual's tolerance, until 3 or 4 hours daily are spent in the perpendicular position. After the patient becomes accustomed to the inverted position, the drainages may be consolidated into 2, but not more than 3, daily periods of from 1 to 2 hours each, depending upon the age and general condition of the patient. If the last drainage is taken just before bedtime, it will not be necessary to elevate the foot or head of the bed for night drainage. It is unnecessary and dangerous to attempt to get drainage upon a sleeping patient as infection may be carried to the sound lung. The patient should be trained to sleep either on the back, abdomen, or the

affected side. If the 2 main bronchi can be kept on the same horizontal plane, the chance of infecting the contralateral lung will be greatly decreased.

There are several drainage beds or "troughs" on the market that can be used to raise or lower the patient or tilt him from side to side mechanically, to facilitate drainage from any part of the lung.

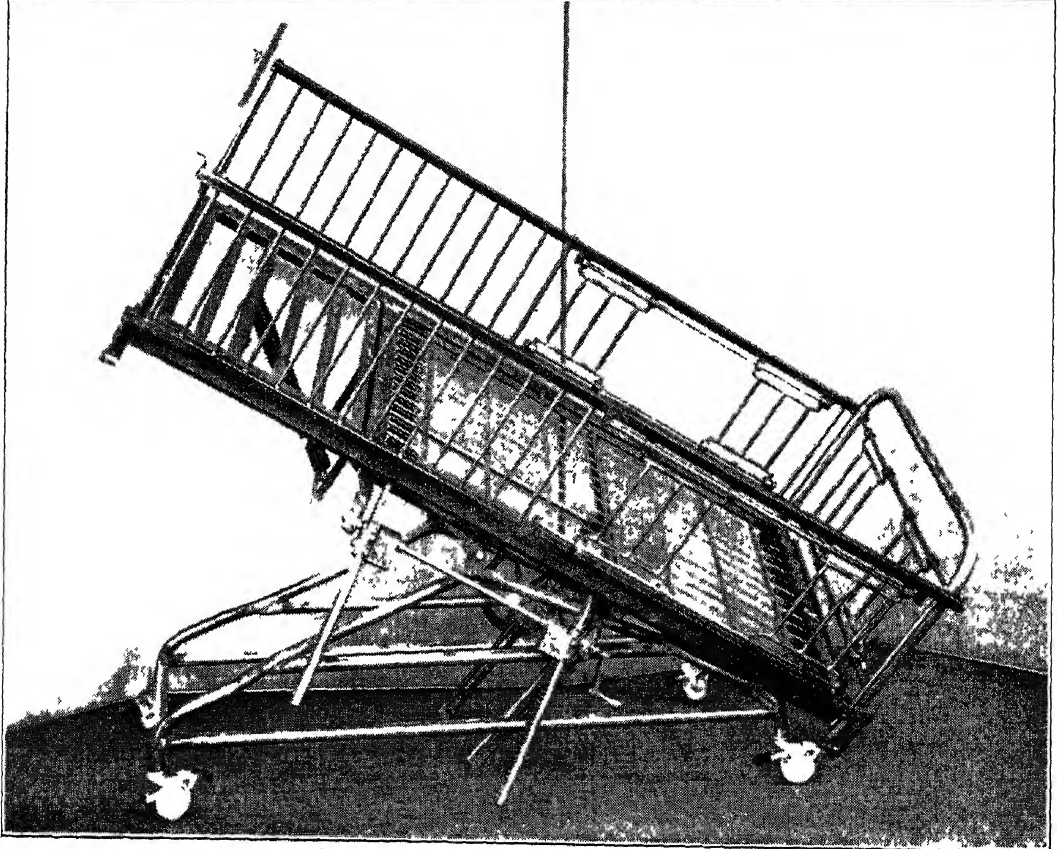
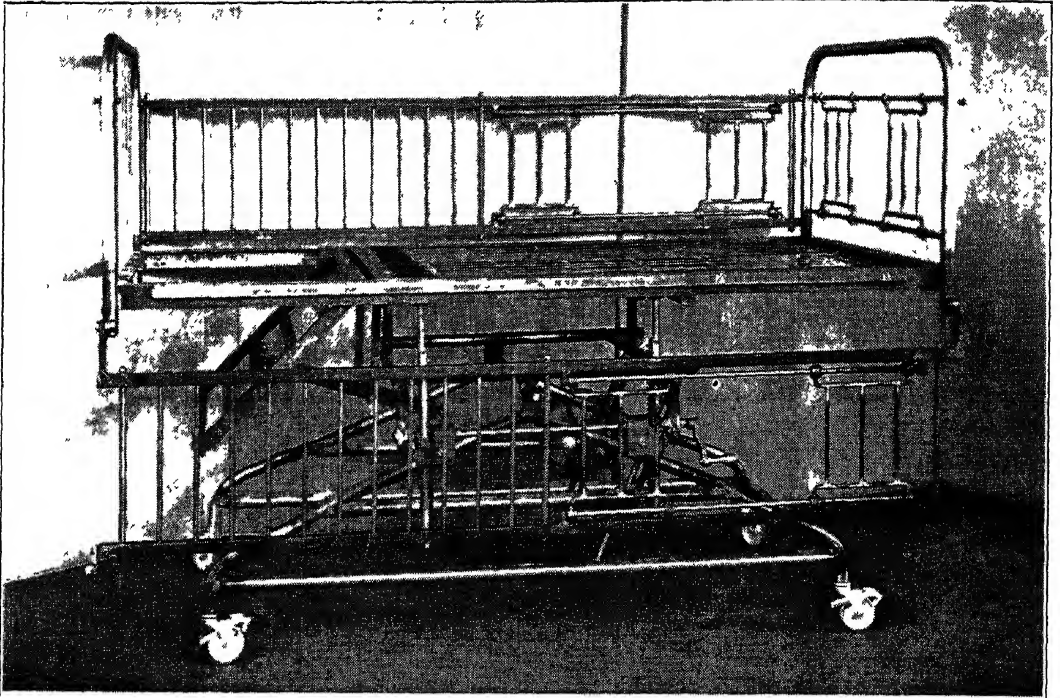
Postural drainage is of especial value for patients that are poor surgical risks due to age or debility, and even a moderate amount of drainage may give surprisingly good results.

If the patient expectorates blood before or after institution of the drainage, the drainage may be continued if bleeding is sporadic and does not increase.

THORACIC SURGERY

Selective Thoracoplasty with Lung Mobilization

Conservative Goal in Permanent Collapse Therapy—R. H. Overholt⁵² reports on 763 thoracoplasties performed on 370 patients during the 5 years that the department of thoracic surgery has been established in the Lahey Clinic. During the first half of this period selective thoracoplasty was used and during the latter half thoracoplasty with lung mobilization. The group represents a consecutive series of patients operated on by the same surgical team. The number of seriously ill patients accepted for thoracoplasty has been increased, yet the risk of operation has steadily declined. Of those in the poor risk group, 60 had bilateral cavitation. Of the 206 patients in the "good chronic" group, 89.5 per cent were definitely benefited by the procedure, 51 per cent are already back at work, and 25 per cent are in various sanatoriums with their disease quiescent.



DRAINAGE BED Specially constructed by the Scanlon-Morris Company, Madison, Wisconsin. (Am. Rev Tuberc. 38 660 (Dec) 1938)

or arrested. In the poor risk group 24 per cent are working and the condition of 26 per cent is quiescent or arrested. It was found that 69 per cent were benefited by operation. In the entire series 121 patients were completely rehabilitated. The possibilities are that eventually the condition of 248 (80 per cent) of the 307 patients whose treatment has been completed will be classified as apparently arrested and that they will be able to carry out varying degrees of activity. The results suggest that thoracoplasty is the most valuable of all permanent collapse procedures. Selective yet adequate collapse of the diseased lung and conservation of the uninvolved lung should be the ideal in permanent collapse therapy. The extent of the decostaliation can be reduced by mobilization of the upper lobe at the time of the first-stage operation. A delay between stages is an important factor in planning the most conservative operation.

Stabilization of Intrathoracic Pressure in Surgery

E. Rehn⁵³ believes that safety and progress in thoracic surgery are coincident with the control of intrathoracic pressures. Practical control must be based upon known and accepted laws of physics. The rise and fall of intrathoracic pressure has a significance other than its direct action upon the breathing and circulatory mechanism. With the contraction and expansion of the lung, impulses are set up which control and direct the respiratory mechanism. In this reaction, every change in intrathoracic pressure is projected to the active respiratory mechanism (Hessian reflex).

The surgical stabilization of the intrathoracic pressure can be produced in several different ways:

1. By maintaining the normal differences in pressure;

2. By the artificial production of adhesions between the visceral and parietal pleura. This may be done either by the use of the Mikulicz tampons as recommended by Sauerbruch, or by pneumopexy. The second method is possible only if the first method is active; this is, the lung may not be collapsed;

3. By artificially fixing the upper anterior mediastinum, either intrapleurally or extrapleurally.

It is well known that one can safely perform intrathoracic surgery if the mediastinum is fixed and will not swing from side to side.

To investigate the possibilities of stiffening the mediastinum artificially, a demonstration of the mediastinum was required, and mediastinography was developed. Kymography, which can be done with or without the injection of 5 cc of abrodil, is recommended. Injection of this substance is valuable as the outer borders of the mediastinum may be fixed by adhesion, while the inner portion is free to move. If this is the case and the adhesions are freed, a catastrophe may occur.

For stiffening the mediastinum, *vivokol* appears to be better than salt solution, but it is not sufficiently viscous. Polyvinyl alcohol is a more suitable substance. It not only fills all requirements, but possesses qualities which make it valuable for all forms of packs. Polyvinyl alcohol is the basis of Braun's syntophyl, first described by Hermann and Haenel, and is related to synthetic rubber. It is absorbed by the tissues, and has a beneficial specific and non-specific effect upon tuberculous infection. The faculty of resorbility is also possessed by its solvent water. The pack contains 94 per cent water, is of rubber consistency at body temperature, and is

liquid at from 45 to 50° F. It can be introduced by either gravity or injection with a syringe. It hardens rapidly. It can be readily sterilized by heat. Careful investigations by Pfannenstiel have shown its entire indifference to all human secretions. By the addition of medicaments, bactericidal and other activities can be induced.

Animal experimentation showed reactionless healing of the injected area. The absorption takes place from the surface by slow phagocytosis. When polyvinyl is injected into the mediastinum of a cat with a large thoracic window, mediastinal flutter stops almost immediately. With 20 cm injected into the mediastinum a large window may be opened into the chest without fear of mediastinal flutter. This same amount will produce a stiffening of the mediastinum in the human.

In 1 case there was a traction diverticulum of the esophagus at the level of the bifurcation. The mediastinum was stiffened preoperatively, which made it very easy to operate with a collapsed lung. The lung was expanded before the thorax was closed. Cure was obtained.

In another case the mediastinum was also stiffened. Chondromyxosarcoma with involvement of the lung was found. The thoracic wall was removed and the lung was partially resected. There was an open pneumothorax. The patient easily withstood a bad phlegmonous pleural infection.

In view of the excellent results obtained in these 2 cases the stiffening of the mediastinum should be used when it is difficult to maintain the normal differences in the intrapulmonary pressure, or when an open pneumothorax may be expected in the postoperative course. This method should be used in all cases of pulmonary collapse when the kymo-

gram reveals a mobile mediastinum or when this condition is merely suspected. It is also of value as packs in thoracic surgery. Animal experiments showed it to be reactionless in the pleural and extrapleural spaces. If more than one-half of the thoracic space is filled with the material, care is required to observe the amount of exudate. This can, however, be removed by paracentesis.

The physical action of the pack demanded clinical proof and the following case afforded the opportunity to study this. The patient presented a pyopneumothorax following rupture of a cavity into an oleothorax. He was in an asphyctic condition from a bad bilateral phthisis, complicated by myocarditis. After the pleura was emptied and filled with polyvinyl, the diseased half of the lung could be immobilized. The cyanosis decreased and the pulse rate improved. After 11 days the patient died of myocarditis. Autopsy showed the lung to be covered by the pack which separated it from an empyema. The immediate picture after the injection was as fine as is seen following a pneumothorax performed under the most favorable circumstances.

Following this unquestionably good result, the method was introduced whenever collapse therapy was indicated, especially in pulmonary tuberculosis. It was used in combination with partial thoracoplasty, apicolysis, and for the purpose of making a pack in bronchiectases and an inferior intrapleural pack for collapse of the lower lobe. This shows the universal action of the pack.

PLEURISY

Treatment—*Formation of Adhesions Following Pleurisy with Effusion*—P. Leifer⁵⁴ states there is a correspondence between the type of inflam-

matory processes in pleurisy with effusion, of tuberculous origin, and the extent of the adhesions formed. The more severe the pleuritic inflammations the more copious the effusion, and the longer the latter remains within the cavity the more it becomes inspissated until fibrinous layers, the foundation of adhesions, are formed. If the tuberculous foci are present in the pleura the inflammatory and effusive processes will be greatest; if the influence is less direct (through bronchial pneumonia or the bronchial lymph nodes) the pleurisy will be less severe. The formation of adhesions do not have a favorable immunobiologic influence on the tuberculosis and is to be combated. Adhesions may have definitely unfavorable consequences, circulation may be impaired by the unilateral constriction of the thoracic organs, the crippled lung may show greater susceptibility to bronchopneumonia, and the presence of adhesions may make it impossible to perform a needed pneumothorax. Formation of adhesions is best minimized by frequent punctures which counteract the tendency of long standing effusion to thicken into fibrinous layers. Repeated puncture, even if it cannot prevent adhesions, can limit their extent.

Clinical and roentgen follow-up studies in 50 of 150 cases in which repeated punctures were done showed slight adhesions had formed in 41 cases, adhesions were almost completely lacking in 4 and they were extensive in only 5

TUMORS OF TRACHEO-BRONCHIAL TREE

Etiology—C. Jackson and C. L. Jackson⁵⁵ states that inflammation is an etiologic factor in some tumors, though just why a rounded tumor-like contour, instead of a diffuse fibrosis, should be a more frequent result in the bronchi than

elsewhere has not been positively determined. The frequency of the rounded contour is contributed to the cylindrical form of the bronchi together with their physiologic movements as a moulding factor. The mechanism somewhat resembles that of the pharmacist's pill roller.

The cause of granulomata in some cases is specific infection, for example tuberculosis, syphilis, spirochetosis, blastomycosis and actinomycosis. A number of cases of epithelialized pedunculated tuberculoma of the tracheobronchial tree have been found in patients with long-healed pulmonary tuberculosis. A number of cases of hematoma of the bronchi have been seen and the capillary rupture attributed to cough.

Pathology—A benign growth is one that does not metastasize and whose cells do not infiltrate among adjacent normal cells. Benign as applied to a growth in the tracheobronchial tree is not synonymous with innocent inasmuch as such a growth may cause death primarily by asphyxia, or secondarily by the suppurative disease caused by its obstruction to ventilation and drainage. Some of the usually benign growths are sometimes encountered in malignant forms. Bronchoscopy has shown that histologically nonmalignant tumors are relatively common, though not quite so frequent as malignant growths.

Tumors and tumor-like conditions have been found such as Angioma, hematoma, adenoma, myoma, myxoma, papilloma, fibroma, fibrolipoma, lymphangioma, lymphadenoma, lipoma, echondroma, osteoma, chondrostoma, retention cyst, amyloid tumor, aberrant thyroid tumor, specific granuloma and nonspecific granuloma. Chondromata and osteochondromata may be benign but are prone to develop malignancy, and by sarcomatous or other changes, even

metaplasia. Edematous polyp and other more or less tumor-like inflammatory growths are occasionally encountered, and are of the utmost importance because of the atelectasis, drowned lung and suppurative conditions they produce.

Histologically, most of these growths do not differ greatly from the same growths encountered elsewhere, but some of them are quite different. One of these peculiar growths is an adenomatous tumor that when first removed by the bronchoscopist was classed as adenocarcinoma by most of the histopathologists. After these growths had been arrested in a number of instances by bronchoscopic removal and in other instances by roentgen-ray treatment, some histopathologists revised the classification and called the tumors benign adenomata.

One pathologically important peculiarity of benign growths in the tracheobronchial tree is that, though small, they set up diffuse destructive secondary changes in the lung out of all proportion to their size. In this there is an anatomic factor in the relatively small diameter of the bronchi, and a physiologic factor in the dependence of the resistance of the lung largely on ventilation and drainage.

As discovered bronchoscopically, the obstruction of a bronchus by a tumor is of 3 types, mechanically similar to the valves in air pumps, namely, a stop-valve, a check-valve or a by-pass valve. The stop-valve action is complete occlusion; it slowly results in atelectasis of the distal area as the air is absorbed by the circulating blood. In the lungs the set of the check-valve mechanism against outflow produces emphysema in the distal area. If the set is against inflow the lung is deflated by the pumping out of air, and atelectasis develops rapidly.

Air cysts communicating with the bronchi have been seen in a number of

instances. Cystic growths of the bronchial mucosa were in some instances of the retention type and in others of the teratomatous type, containing hair and amorphous material. The larger cysts were associated with suppuration. Small cysts contained glairy mucoid material.

The wall of removed small retention cysts of the bronchial mucosa did not differ much histologically from those so common in the larynx.

Symptoms—The symptoms depend upon the stage at which the patient is seen. In the beginning the patient is symptomless. A wheeze heard at the open mouth, not at the chest wall, is usually the earliest symptom and is almost always present later. The sound is quite similar to asthma, so much so, in fact, that many patients had been regarded as having asthma.

Cough and slight mucoid expectoration appear as the growth progresses, usually becoming more troublesome when the tumor occludes the bronchus. Dyspnea independent of exertion does not occur from obstructive atelectasis of a lobe or even of an entire lung. In 1 case a mass of epithelialized granulomata occupying the orifice of the right bronchus and causing obstructive atelectasis of the entire right lung did not produce dyspnea except on exertion. On the other hand, a histologically similar tumor mass at the bifurcation, which occupied part of both main bronchial orifices, caused intense nocturnal attacks of dyspnea, simulating asthma so closely that the patient had been treated for months under this erroneous diagnosis. Complete relief of these symptoms followed bronchoscopic removal of the tumors.

Hemoptysis is a symptom of benign bronchial tumor and is quite constantly associated with adenoma. Strange as it may seem, benign growth as a diagnostic

possibility is omitted in many of the textbooks in presenting the subject of hemoptysis.

Diagnosis—Benign bronchial tumor as a clinical entity developed from incidental discoveries at diagnostic bronchoscopies. For this reason the first impulse is to dispose of the subject of diagnosis with advice to have a bronchoscopic examination. Though this is good advice it would not be good literature. Moreover, to follow it would not be good clinical procedure. Equally bad would be an attempt to make a diagnosis from the symptoms, because none is characteristic, let alone diagnostic.

Orderly procedure calls for:

1. Anamnesis, with careful record of symptoms
2. General medical examination with record of all physical signs (interpretation may well be postponed until later).
3. Taking of specimen for serologic test and blood picture record.
4. Repeated sputum examinations
5. Roentgen-ray examination.
6. Diagnostic bronchoscopy.
7. Bronchoscopic biopsy.
8. Histologic examination.

Physical signs in case of uncomplicated, nonobstructive bronchial tumors are negative. Just as a growth reaches a size sufficient to cause the slightest degree of obstruction the physical signs are definite and of great importance.

The earliest of the physical signs of bronchial obstruction, whether caused by a tumor or anything else, is a wheeze heard at the open mouth. This has so often been mistaken for asthma prior to admission of the patient that in order to call attention emphatically to the necessity for differentiating it from a true asthmatic wheeze it is called the "asthmatoïd wheeze."

Next in importance to the asthmatoïd wheeze heard at the open mouth are the physical signs of by-pass valve obstruction, chiefly harshness of breath sounds

distal to the tumor. Then come the physical signs of check-valve obstructions producing atelectasis and emphysema. These also are distal to the tumor. When the physical signs show atelectasis or emphysema, bronchial tumor should be placed first among the diagnostic possibilities. Diagnostic bronchoscopy is the only means for determining the character of the lesion or substance concerned in the check-valve mechanism.

Of diagnostic importance equal to that of the physical signs and the diagnostic bronchoscopy is the roentgen-ray examination. It is true that small endobronchial benign tumors do not cast a shadow, yet fluoroscopy is the best means for demonstrating the differentials in aeration present in all cases of check-valve obstruction, a form of obstruction which always raises the question of bronchial tumor. Moreover, in case of large benign growths causing stop-valve or check-valve compression stenosis, the growth usually shows as a shadow in the roentgenogram and the compression of the bronchus can be demonstrated by insufflation of bismuth subcarbonate or the instillation of lipiodol into the tracheobronchial tree.

Pitfalls in diagnosis are due to delay or failure in availing one's self of the information obtainable by diagnostic bronchoscopy.

Bronchoscopic biopsy is the only means known to medicine today for the determination of the character of a benign bronchial tumor.

Prognosis—Some benign endobronchial tumors are fatal, primarily by asphyxia or secondarily by the sequential suppurative disease of the lung. Almost all benign endobronchial tumors and tumor-like formations can be removed bronchoscopically, and the prognosis as to life in such cases is good. Recurrence

is a possibility, especially in cases of lymphoma and papilloma, in papilloma and some forms of granuloma new growths may appear at new locations after removal of the primary growth. In such cases reappearances usually cease after repeated superficial removals. The prognosis of benign adenoma is good provided the patient be seen occasionally in order to detect and treat recrudescence or recurrence early.

Treatment — Large peribronchial compressive growths, if radical treatment is really required, are dealt with by *external surgery*. This applies particularly to epidermoid cysts causing suppurative destruction of pulmonary tissue. It is mechanically feasible bronchoscopically to penetrate compressed, uninvolved bronchial wall to reach a benign peribronchial growth, but the advisability of doing so is questionable. In cases of an cyst, treatment was not indicated except when the interior was infected and suppurating. The large teratomatous cysts were associated with profuse suppuration and were operated upon by the surgeons who referred the patients for diagnostic bronchoscopy. One patient admitted with a diagnosis of bronchiectatic abscess was found, after a number of bronchoscopic aspirations of enormous quantities of foul pus, to have a large epidermoid cyst, external operation was required for removal.

X-ray treatment externally applied is usually effective in glandular tumors, particularly lymphoma, adenoma, thymic and thyroid tumors. Bronchoscopically applied physical therapy has been useful in some instances.

Bronchoscopic Removal — Endobronchial benign growths of any size can be removed bronchoscopically. The indications for the procedure are any signs of bronchial obstruction or any suspicion that an unobstructive tumor

will become obstructive but not occlusive. The slightest sign of approaching obstructive atelectasis or approaching obstructive emphysema, no matter how small the area manifesting such a sign, calls for bronchoscopic removal, unless there are preponderant contraindications. To wait for occlusion would be a mistake.

Apart from any of the indications mentioned, any small tumor formation encountered bronchoscopically may well be extirpated because of its potentialities. Impaired drainage even of normal secretions is an important indication for removal of any tumor, however small. Apart from obstruction by bulk, a tumor usually has no cilia; drainage efficiency is proportionately impaired.

The most important *contraindications* are a strongly positive serologic test, a high, irreducible hypertension, or any organic disease that of itself lessens the patient's life expectancy. Less serious degrees of hypertension are not a contraindication. Hemorrhage unless exsanguinating is not a contraindication. In some cases it is advisable to postpone removal of a growth until after transfusion and other appropriate methods have titided the patient over the anemic danger point. In some cases, however, bronchoscopy may be indicated for hemostasis.

The *technic* of introduction of the bronchoscope is well established. In most instances forceps are the preferable instruments for bronchoscopic removal of benign tumors. The 2 forms most useful are the cupped forceps of tubular mechanism and the sharp-cornered basket punch forceps. The latter have a clean cutting, shearing mechanism that must be used with utmost precaution and precision to avoid danger of invading normal tissues, they are needed only in case of chondroma, osteoma and other very firm growths. The cupped forceps

are quite safe if used with delicacy and keenness of touch. Plain slender-jawed forceps are useful chiefly as dilators.

Small pedunculated tumors may be completely removed, using great care to avoid any damage to basic normal tissues. In case of large growths or sessile small growths, it is usually preferable to know the histologic structure of the tumor. In these cases, bronchoscopic biopsy is the proper preliminary.

Small inward projecting retention cysts should be *amputated* bronchoscopically. Small mucous cystic cavities should be evacuated by inserting slender forceps jaws closed and then expanding them to distend the orifice. If reaccumulation occurs repeatedly, 1 edge of the orifice may be nipped out. Nonspecific granulomata should be *nipped off superficially*. Specific granulomata, including fungoid growths, may be *removed*; but removal of epithelialized syphiloma and tuberculoma may be *contraindicated* by general conditions. Papillomata are usually multiple, they should be *scalped off superficially*, including every little bud, but neither forceps nor caustics should be used on the base. Radical extirpation is useless and unnecessary and involves needless risk. New growths may appear in new locations no matter how radical the primary extirpation may have been. *Superficial scalping* with the cupped forceps will remove all papillomatous tissue yet leave all normal tissues unharmed.

The word scalping is used here in contradistinction to cutting, biting or even nipping. The cupped jaws and delicate touch enable the operator's fingers to distinguish normal tissue by its resistance, after the jaws have passed through papillomatous tissue. When this resistance is felt, the forceps are not compressed further but are gently withdrawn,

allowing the 2 cups to slide off the normal base without injuring it.

Some of the pitfalls in external operation can be avoided by co-operation with the bronchoscopist. Pitfalls in bronchoscopic removals of benign growths are almost all avoidable by conservatism, caution and utmost delicacy of touch.

TUBERCULOSIS OF CHILDHOOD TYPE

Clinical Significance—S. H. Snider⁵⁶ states that childhood type tuberculosis in the chest includes all tuberculous infections in chest prior to the development of the secondary pulmonary invasion, or adult type tuberculosis.

When the infection first takes place in the lung tissues, probably the most common route of infection, a Ghon tubercle is formed. This at first is not a true tubercle, but partakes more of the nature of an inflammatory reaction. This infection is usually followed in about 10 days to 3 weeks by the development of allergy or sensitization to the protein products of the tubercle bacillus. At the same time, the infection spreads along the lymphatic channels from the Ghon tubercle toward the hilum lymph-nodes. These become infected and enlarged and true tubercle formation takes place in them. Later the infection may spread peripherally from the hilum lymph-nodes to the lymphatics in other parts of the chest and especially to the lymph-nodes of the opposite lung, to the mediastinal lymph-nodes and lymph-nodes in other parts of the body. So long as the disease remains restricted to the lymph-nodes and true secondary pulmonary invasion has not taken place, the disease is to be classified as childhood type tuberculosis.

The phenomenon known as allergic reaction plays a large and definite part

in the pathology and symptomatology of the disease. It is altogether likely that fever, tachycardia, fatigue, and loss of appetite are due to this allergic reaction. This seems to be proved by the fact that the injection of dead tubercle bacilli, or their protein derivatives, will produce exactly the same symptoms of toxemia.

Complications — Occasionally, it is believed, a hilum lymph-node ruptures into the bronchus and floods the bronchial tree with tubercle bacilli, in which case acute tuberculous pneumonia may occur. This explains the influenzal or pneumonic type of tuberculosis and accounts for the sudden onset of adult type disease in a patient who was apparently in perfect health before. There may be hematogenous spread, giving miliary lesions more or less throughout the body, resulting from the discharge of tubercle bacilli into the blood stream. Thus, there are 3 types of transition from childhood to adult type of disease — the insidious or peribronchial spread and the sudden pneumonic and miliary spreads. The latter types of extension cannot be accurately forecast, but the former, or insidious type of spread, can be seen in its early stages and measures can be taken to prevent further ravages. Every child who has a positive tuberculin test should have periodic x-ray examinations, for by so doing the onset of adult clinical tuberculosis can frequently be foretold.

Exogenous reinfection is also a possibility that must be considered. While its part in the development of adult type tuberculosis is not altogether clear, it must be regarded as a danger, and every child should be protected against infection or reinfection as far as possible. Some authorities seem to be of the opinion that all, or nearly all, of the adult type tuberculosis is a sequel to exogenous reinfection. However, most of the

adult type tuberculosis arises directly from the childhood type.

Diagnosis — Since allergy requires about 10 to 20 days for its development, there is no very accurate means of differential diagnosis of the tuberculous lesion during the first few days of its existence. After 2 or 3 weeks, the tuberculin test usually becomes positive and may be used as positive evidence of tuberculous infection. The positive test gives us the very valuable information that tuberculous infection is, or has been, present in the body. It does not differentiate the childhood type from the adult type of infection, nor is it an indicator of activity and progress of the disease.

Allergy lasts for a long time, but not necessarily for a lifetime, as is indicated by the fact that the incidence of positive tuberculin tests is far less than the incidence of autopsy-proven tuberculous infection. The tuberculin test is used purely as a diagnostic measure and means nothing more than that the individual has been infected with tuberculosis. False positives are practically unknown, so it is pretty safe to say that the individual with a positive Mantoux test has been infected.

Since the positive Mantoux gives no information about the extent and progress of the disease, it is necessary to use other means to determine this point. For this purpose, the roentgen-ray plate and fluoroscopic examination are of great value. Roentgen-ray plates seldom disclose the Ghon tubercle, for that is usually healed or resolved by the time the patient comes for observation. Frequently, however, the Ghon tubercle has undergone calcification and left a calcified node as evidence of its having existed. This may be termed Ghon nodule. Thickening along the peribronchial tissues leading from the Ghon nodule toward the hilum is frequently seen and

thickening and raggedness of the hilum are common. Retrograde peribronchial thickening in other directions is frequently seen and, if this shows definitely hazy margins, it is usually safe to say that pulmonary invasion is taking place. Then we have the adult type of the disease. This is the manner in which the insidious peribronchial spread occurs, the transition from childhood to adult type of the disease.

Prognosis—Since the approximately 85 per cent of adults show scars of tuberculous lesions of the childhood type, and since the incidence of positive tuberculin tests in adult life is about 30 to 40 per cent, we may conclude that the major portion of the infected individuals have healed the tuberculosis and lost their allergy. Since about 7 per cent of all deaths are due to tuberculosis and 85 per cent of the community are infected, we may conclude that the ultimate death rate from childhood type tuberculosis is about 1 in 12.

Altogether, the picture presented by tuberculosis is much more hopeful than it was a few years ago, and increasing knowledge of its manifestations and increasing use of measures against it may be expected to still further reduce the ravages of this disease.

Treatment — Physical findings in these cases are usually negative, with the exception of fever and tachycardia. A mild degree of fever does not demand that the child be put to bed for absolute bed rest, but that he should be put on *restricted activities* and given *plenty of good nourishing food* and *natural*, not synthetic, *vitamins A, B, and D*. Even with the use of such a program some patients are certain to break down with the adult type of the disease, but the breakdowns will be fewer in number and will be diagnosed early and present much less serious prognostic problems.

EXOGENOUS PULMONARY TUBERCULOSIS IN ADULTS

Etiology—E. Filla⁵⁷ states that exogenous superinfection is a frequent cause of pulmonary tuberculosis in adults ranging in age from 15 to 25 years and rare after that. The disease shows typical early tuberculous infiltration of Assmann's type. When the bacilli are virulent or the patients are in a state of receptivity, bronchopneumonic lesions which follow a serious evolution develop. Tubercle bacilli of exogenous or endogenous origin may remain for a long time in the body of a person with good immune-biologic resistance, without causing tuberculosis, or causing only transient nontuberculous symptoms. The behavior of the large number of tubercle bacilli that enter the body from superinfection depends on the receptivity of the patient when superinfection takes place and for a long time after that, as the latent disease may develop as soon as infection becomes stronger than immunity.

The dynamic energy of tuberculous infection or superinfection plays the most important part in the development of tuberculosis in children. For the development of the disease in adults, the individual factor plays the most important part.

Incidence and Prevention of Tuberculosis in American Schools and College—E. R. Long⁵⁸ states that studies continued over a decade indicate that the proportion of elementary and high school children positive to the tuberculin test is steadily falling. In the less crowded communities the drop is more striking than in large, congested cities. The incidence in rural communities is generally significantly lower than in urban areas, and differences within

the same community are always found corresponding to the economic level.

Important tuberculous disease is first encountered in an appreciable extent in high school students, where the combined incidence of latent and manifest disease varies from 1.5 to nearly 3 per cent, being higher among girls. Important disease demanding care occurs in from 0.5 to 1 per cent of these children. Active programs for the early detection and control of tuberculosis in schools now operate throughout the country. The basic principles of these programs are mass tuberculin testing, x-ray examination of the positive reactors and provision of suitable care for those found to have lesions. In the colleges about 6 students per 1000 have tuberculosis of the adult type. The average incidence for the country as a whole is from 30 to 35 per cent. A marked variation occurs geographically, students from the great central portion of the country having a relatively low incidence. Tuberculosis is recognized as the most serious disease of the college period yet as insidious in onset, requiring routine mass measures for its detection. Most of the lesions now discovered are in the minimal stage. Students of medicine and nursing are now known to be subject to a special hazard. The danger for medical students seems greatest during the third and fourth, or clinical years, suggesting that tuberculosis acquired in the medical school usually is exogenous. Most nurses who are tuberculin-negative on beginning training become positive to tuberculin during their course. The incidence of clinical tuberculosis is also proportionately high as compared with other professional or working groups at the same age, both during the period of training and in the first years after qualification.

The Environmental Factor in Relation to High Negro Tuberculosis

Rates—R. B. Roth⁵⁰ studied the figures from the United States Army in order to overcome the differences of environment of the Negro as related to tuberculosis. These figures equalize the environmental factor. They are made up of the absolute numbers and the rates for tuberculosis morbidity and mortality among the enlisted men in the continental United States alone. For the period (1922 to 1936) under consideration the total white death rate is 0.24 per 1000 enlisted men, while the Negro rate is 0.99. When this evidence is considered in conjunction with other environmental surveys and in view of the clinical and pathologic differences which are to be recognized in the 2 races, environment cannot be held to explain the differences in susceptibility to the disease which the 2 races so generally manifest. The fact that tuberculosis, as it is handled by the army, accords so closely to the standard set in the Framingham experiment makes it possible to generalize on the rôle which environment does play in tuberculosis in civil life. Diagnosis in the army is highly developed. The average death rate from tuberculosis in all troops combined for the 15 years was 0.28 per 1000. According to the figures of the National Tuberculosis Association, the national death rate in 1927 for males in the age group corresponding roughly to that represented in the army (20 to 49 years) was 1.17 per 1000. A great deal of this difference is undoubtedly due to the fact that in the army a selected group of men is dealt with, but certainly environment can be held responsible for a considerable part of it. Even under optimal environmental conditions there would be the same difference in rates. A slightly greater percentage of Negroes might be expected to contract the disease, but a considerable greater percentage of them would die from it.

Complications — *Erythema Nodosum* an Allergic Reaction in Tuberculosis—N. A. Tsukkerman and P. T. Rybak⁶⁰ point out that children suffering from erythema nodosum react to tuberculin with great intensity. Thus the sensitivity to tuberculin in such children was in many instances increased to the point of reacting to dilutions of 1:1,000,000, whereas reactions to dilutions of 1:100,000 or 1:1000 is the rule. The sensitivity to tuberculin is moderate or negative before the appearance of the eruption. With the rise of the temperature and the appearance of the eruption it becomes greatly heightened. The eruption thus coincides with hyperallergy. At the same time pathologic increase of roentgenologic shadows at the root of the lung become demonstrable. Erythema nodosum is not to be considered a tuberculous lesion. From an anatomic point it is not a tuberculous process. While children with erythema nodosum react to nonspecific bodies as well, such reactivity is transient, whereas the reactivity to tuberculin persists. In 14 children recently recovered from erythema nodosum, a positive reaction was found to the tuberculin. In 12 it was intense, exhibiting vesicles on the surface of the papules in some. A diagnosis of tuberculous infection was made in all of the group. Of these, 8 had tuberculous bronchoadenitis, 2 had pulmonary tuberculosis, 2 developed pleurisy with effusion, 1 tuberculous meningitis and 1 an allergic state. Roentgenologic examination showed tuberculous infection in all. Contact with open cases of pulmonary tuberculosis was found to have existed in 7. Every case of erythema nodosum in a child must be regarded as one in the acute stage of tuberculous allergy and should be observed as such by the tuberculosis dispensary.

Further Observations on Hypophyseo-Endocrine Reactions in Tuberculous Infections—L. Koster, and R. de Boer⁶¹ describe a syndrome which occurs in tuberculosis and which is characterized by obesity, erythremia, hypertension, purplish red striae, hyperglycemia, glycosuria, hyperthermia, moderate increase in the cholesterol content of the serum, increase in the basal metabolism and genital anomalies. Because these symptoms are the same as those that have been observed in hypophyseal disorders, hypophyseal anomalies have been regarded as a causal factor. Fourteen cases were reviewed. The cholesterol ester rate and the lipase content of the serum was found to be increased in these patients which is an indication of a hyperfunction of the hypophysis or at least of some of its elements. This hypophyseal disorder is especially frequent in tuberculosis and is the result of the fact that the immunity reactions of tuberculosis are entirely different from those of other infections. The hypophyseal hyperfunction is a form of defense reaction.

Mucosal Tuberculosis of the Bronchi and Trachea—P. C. Samson⁶² states that mucosal tuberculosis of the bronchi and trachea is a complication of active pulmonary tuberculosis which often may have serious consequences, and its recognition is of importance.

Clinically, tuberculous tracheobronchitis may be suspected by the correlation of suggestive symptoms and roentgenographic findings. With few exceptions, bronchoscopy should be used as the final step in diagnosis and as a guide to therapy.

Best results have been obtained by the use of high frequency electrocautery. Special electrodes have been designed to use through the bronchoscope. Finally, lobectomy, pneumonectomy or external

drainage of a tuberculous cavity occasionally must be considered in dealing with the secondary effects of high grade bronchial obstruction.

TUBERCULOUS TRACHEO-BRONCHITIS

Etiology—W. Warren, A. E. Hammond, and W. M. Tuttle⁶³ state that in some cases, bronchial ulceration may be a manifestation of poorly resisted disease.

Pathology—In 74 patients with tracheobronchial tuberculosis, the ulcerative lesions fell into 2 types: the discrete ulcer and the granulating ulcer. The granulating type has occurred most commonly about the orifice of the main bronchi, on the carina and in the lower portion of the trachea. Healed and ulcerating stenosing lesions have been observed. Tuberculoma or tuberculous granuloma has been observed in four patients.

In 3 patients there was a diffuse hyperemia of the bronchial mucosa with moderate mucosal edema.

Biopsies were performed in 14 cases in which the lesion was large enough to obtain tissue safely for study. In 4 instances, the lesions were tuberculomas and in 10 were of the granulating ulcer type in which the growth of granulation tissue was great enough to obtain a bite. The specimens for biopsy obtained from the 4 patients in whom a tumor mass was present were all tuberculous granulomas. The remaining biopsies in cases in which a granulating ulcer was present showed tubercles in 4 of the 10 cases.

Clinical Course—The healed stenosis represents a healed ulcerative lesion in which the reparative process has partially or completely occluded the lumen. The ulcerostenosis represents a stage

midway between the healed, cicatricial stenosis and the granulating ulcer.

Diagnosis—There is no clear-cut ground for the assumption that this is a tuberculous lesion other than that in 2 patients the sputum was positive although neither had a demonstrable lesion to account for the tubercle bacilli.

In these 14 cases, there has been no evidence that removing small pieces of tissue from these lesions has led to any untoward results. The danger of perforating the bronchial wall in these cases outweighs the value of the additional information obtained by biopsy.

It is better to err on the side of performing a bronchoscopic examination on a patient with a normal bronchus when the diagnosis is in doubt than to leave the ulcer untreated.

Prognosis—In the 74 cases, there have been 6 deaths. These have not been due to the tuberculous bronchial ulceration but to the severity of the parenchymal lesion.

Treatment—In some instances such lesions heal spontaneously, but, when they are treated early, healing occurs and leaves little or no trace, when the ulcer is old and deep, stenosis has already begun to develop and this is an irreversible process.

TUBERCULOSIS IN THE MALE GENITAL TRACT

Present-Day Conception—E. A. Miller⁶⁴ states that genital tuberculosis is a secondary infection; that the genito-urinary system can never be the portal of entry for a tuberculous infection into the human body. The infection spreads to the genitalia by way of the blood stream, lymphatics, or by continuity of tissue. The original focus of infection is usually the lungs or urinary tract.

Incidence—Of the 1314 male patients admitted to the sanatorium of the Jewish Consumptive Relief Society in the 10-year period between 1927 and 1936, 36 patients suffered from clinical genital tuberculosis, giving an incidence of 2.75 per cent. These figures compare favorably with the 6 cases reported from the Whipp Cross Hospital, England, of 334 patients admitted suffering from tuberculosis, giving an incidence of approximately 2 per cent.

Pathology—Genital tuberculosis may occur at any age and has been reported in patients from 2 years to 67 years. The vast majority of cases, however, occur during the age of greatest sexual activity, in patients ranging from 20 to 40 years.

Clinical Course—There are 2 general theories concerning the pathogenesis of tuberculosis of the male genital tract:

1. That the prostate and seminal vesicles are involved primarily in the urogenital system, and that the disease may remain localized or spread as a descending genital or ascending urinary tuberculosis.

2. That the prostate and seminal vesicles are involved secondarily from other urogenital organs by dissemination through the lumina or walls of hollow viscera connecting them; specifically, ascending genital or descending urinary tuberculosis.

The disease most often starts in the vesicle and prostate but may occasionally start in the epididymis. Genital tuberculosis is primarily a disease of the structures apart from the testis, the orchid remaining intact in the presence of extensive long-standing disease of the epididymis, only becoming involved by extension very late. In the large majority of cases both epididymides eventually show clinical evidence of the presence of tuberculosis though there may be an

interval of some months before this is observed.

Diagnosis—Changes in the scrotal skin are sometimes a valuable guide to correct diagnosis. In tuberculosis there is often loss of elasticity, as shown by the smoothing out of the rugae, and a wasting of the cellular tissues, immediately beneath the dermis. Adhesion of the skin to the epididymis is a well-known sign, as is also a sinus discharging creamy pus. A comparison of the mobility of the 2 testicles is sometimes helpful. The normal organ can be moved freely within its coverings particularly in an upward and downward direction. This movement is often restricted in tuberculosis. In the advanced stages of the disease there is the craggy nodular epididymis and the thickened vas deferens with its bead-like prominences.

Examination of the Urethra, Prostate and Seminal Vesicles—The variety of genital tuberculosis, which is due to an extension of the disease from the urinary tract, commences as a urethritis. The discharge is frequently insignificant; with a secondary infection the discharge takes on the characteristics of that observed in chronic gonorrhea.

The only method available for examination of the prostate and seminal vesicles is that of palpation with the finger through the wall of the rectum. Nodules in the prostate, recognized by sense of touch, indicate extensive involvement of this organ. Likewise, when the seminal vesicles are felt as pencil-like bands extending in an upward and outward direction from the upper margin of the prostate, the prognosis is equally bad. It must be stressed in the earliest stages of the disease a failure to note any changes by palpation in the consistence or size of these accessory sexual organs does not exclude tuberculous invasion.

Coexistence of Renal Tuberculosis—Patients with genital tuberculosis should always have a most thorough examination to establish the possible coexistence of renal tuberculosis, such a combination occurring much more frequently than has been generally recognized

Differential Diagnosis—The difficulty in accurate diagnosis of swelling of the testicle has been emphasized so much, and yet these difficulties are the result of ignorance and incomplete investigation. If the examination is confined to palpation of the genitalia alone it is obvious that grave errors in diagnosis will be made.

There are certain infective processes, both local and general, which may simulate genital tuberculosis, such as the epididymo-orchitis of *Bacillus coli* origin. The presence of the *Bacillus coli* in the urine is sufficient to dispel uncertainty. In this type of the disease the severity of the constitutional disturbances, high fever, etc., followed by sudden acute pain and swelling of the testicle, are sufficient to exclude a diagnosis of tuberculosis. Moreover, an acute abscess of the testicle often occurs, and this is not found in tuberculous epididymitis.

It should not be difficult to diagnose the tuberculous testicle from orchitis due to mumps. The extreme pain and severity of the constitutional symptoms in the latter condition bear no resemblance to the clinical manifestations of tuberculosis.

In lesions due to trauma and torsion, the history of the acute onset and the findings usually limited to the orchid, are indicative of the proper diagnosis.

The 1 disease which simulates tuberculous epididymitis more closely than any other is the low-grade infection which may follow gonorrhea, urethral instrumentation, and cystitis due to pros-

tatitis and other lesions of the lower urinary tract. Again a complete investigation of the bladder, urethra and genitalia, and inquiry into the previous medical history of the patient, will solve the problem.

Syphilis can be excluded by the result of the Wassermann reaction and the absence or decrease of testicular sensation.

In cancer of the testicle, the diagnosis is suggested by the increased weight of the organ, its globular shape, and the presence of enlarged glands in the iliac fossa. At times a hematocele is present, a tuberculous testicle never gives rise to a hematocele, nor does it feel heavier than normal, unless a large abscess is present when the diagnosis causes no difficulty. Malignant disease may occur rarely, in the epididymis only, as a hard nodule, an accurate diagnosis in such cases is extremely difficult.

The presence or absence of a hydrocele is supposed to have an important bearing upon the differential diagnosis of testicular swelling, but is an exaggeration. In all inflammatory lesions of the testicle a hydrocele may be associated. Even in malignant disease when the epididymis becomes involved, a collection of straw-colored fluid may form between the 2 layers of the tunica vaginalis.

Correct diagnosis is aided by exploratory puncture of the hydrocele which permits a thorough palpation of the testicle.

Treatment—*Rest, diet and hygienic outdoor existence*, such as is carried out in a well-regulated sanatorium, are very important. Surgery from a careful resection of definitely localized foci to the complete removal of the seminal tract, besides being uselessly mutilating, cannot be curative.

Heliotherapy is particularly applicable in this type of disease. It arrests the

progress of pathologic change and seems to promise a cure of tuberculosis of the genitourinary tract. One hundred and twenty-eight cases of genitourinary tuberculosis were treated by heliotherapy. Out of 64 genital cases, 26 are clinical cures, 33 improved, 5 stationary. The so-called clinical cures probably should be called arrested cases, since under adverse circumstances, they may again become active, as do pulmonary cases. The results are more certain and rapid and reactivation is less likely to occur if the primary principal focus of involvement of the genital tuberculosis is irradiated directly in addition to local and general radiation treatment.

The procedure is as follows: The prostate gland and seminal vesicles are rayed through a proctoscope with the water-cooled lamp using a special applicator. It is inserted to full depth to ray the seminal vesicles, then it is withdrawn about one-third for the upper part of the prostate, then about a second one-third for the lower portion, always keeping above the external sphincter in order not to blister its mucous membrane. First one side is treated, then the other by changing the direction in which the applicator points. In this way all of the tissues are irradiated, beginning with 5 seconds' exposure which is gradually increased up to 15 seconds for each area.

The scrotum and its contents are given local treatments with the water-cooled lamp just short of the point of blistering the skin. The scrotum is divided into 5 areas on each side and 5 seconds' exposure is given to each, with burner, at contact distance, without overlapping. The time is increased up to 15 seconds as tolerance increases. In addition, general actinic ray treatments are given for their physiological action by heliotherapy according to the Rollier method,

or general body radiations by the air-cooled quartz mercury lamp. The chest is not exposed where there are active soft lesions, but no hesitancy is felt in exposing the chest where there is any fibrosis at all. These treatments are given daily at first, then every other day, when marked improvement takes place.

Other local treatment consists of *removal of free pus* in cases in which the lesion is superficial, and easily accessible. Abscesses of the scrotum should be *aspirated*, the needle being inserted through healthy tissue, and thus into the abscess. The procedure is repeated as often as necessary to keep the abscess drained. *Photodynamic dyes* such as *gentian violet*, or *mercurochrome*, are used by application or irrigation to the scrotum and draining sinuses.

A large number of persons are rendered sterile by genital tuberculous involvement so a *prophylactic ligation* is recommended with removal of a small portion of the vas on the opposite side in selected cases.

After a few days of apparent reactivation, the prostate and seminal vesicles begin to be less tender to pressure, nodules seem to be less firm and gradually decrease in size until only the presence of some fibrous tissue keeps them from feeling entirely normal. It seems that these structures, under direct radiation, yield much more readily than do the scrotal lesions. The epididymitis after a few treatments shows apparently an activation of symptoms. There is a slight recurrence of local pain or aggravation of it if it is still present. The hard indurated areas soften, and soon break down. There is apparently a stirring up of the general system to active reaction in contrast to the sluggishness before, which allowed the smoldering local process to progress slowly.

An abscess develops and discharges. The local diseased area is expelled, the tissues heal, and that is the end of that particular focus. One after the other, these local foci are eradicated in this way until the disease is healed. When the foci are small, they are evidently absorbed without going through the process of breaking down. If the lesion is already an open one when treatment is begun, it readily heals. The mixed infection is quickly sterilized by the bactericidal action of the ultraviolet rays, and the process is then identical with that of the closed lesion. In these cases we believe that healing is hastened by the application of, and irrigation with the photodynamic dyes in contrast to the long, never healing, pus-discharging sinuses in other forms of treatment.

TUBERCULOUS PNEUMONIA AND DIABETES MELLITUS

Report of a Case Treated With Artificial Pneumothorax and Insulin With Marked Improvement

H. C. Shepardson and C. A. Noble, Jr.⁶⁵ state that

1. Tuberculosis occurs 2 to 3 times as commonly in individuals with diabetes as it does in the general population, and the combination of the 2 diseases is on the increase

2. When the diseases coexist, the diabetes usually precedes the tuberculosis.

3. The exudative type of tuberculosis is usually common in tuberculous diabetic patients.

4. Tuberculous pneumonia was of uniformly bad prognostic import.

5. Pulmonary tuberculosis frequently occurs in diabetic patients after coma.

6. Tuberculosis increases the severity of diabetes, and consequently makes the latter disease more difficult to control.

7. Tuberculous diabetic patients can tolerate safely, and should be given insulin, to enable them to maintain a satisfactory state of nutrition.

8. Frequent insulin reactions are to be expected.

9. Artificial pneumothorax is of value. The indications for the use of this procedure in the diabetic patient with tuberculosis are similar to those in the non-diabetic.

10. A case is reported in which a patient with tuberculous pneumonia and diabetes has recovered sufficiently to return to work.

11. In view of the susceptibility of the diabetic population to tuberculosis, all persons having diabetes should be subjected to roentgen examinations and to frequent physical examinations of their lungs.

COEXISTING PULMONARY TUBERCULOSIS AND PRI- MARY CARCINOMA OF LUNG

C. P. Larson⁶⁶ cites 2 cases of co-existing pulmonary tuberculosis and primary carcinoma of the lung. In 1 case the pulmonary tuberculosis was active and in the other there was no evidence of activity. However, the tumor in the second case originated in close proximity to the site of the inactive, healed tuberculous lesion. Both of these cases would tend to substantiate Ewing's opinion that tuberculosis is one of the etiologic factors in the production of primary carcinoma of the lung.

DIAGNOSIS OF TUBER- CULOSIS

Tubercle Bacilli Concentrated in Sputum With Sodium Carbonate—
B. H. Y. Tang⁶⁷ examined 481 specimens of sputum from patients known

to be suffering from pulmonary tuberculosis both by Petroff's 3 per cent sodium hydroxide method and by the sodium carbonate method. (Sodium carbonate in a solution of 7 per cent, allowed to act on the sputum for 30 minutes at a temperature of 65° C., is recommended to replace sodium hydroxide). One hundred and thirty-two other sputum specimens were examined by the direct smear method made from selected portions of the whole sample before being divided into 2 portions and further examined by the 2 concentration methods.

It was found that sodium hydroxide concentration revealed only 4 per cent more positive sputums than direct smears, whereas the sodium carbonate method added 26 per cent. Bacilli are found more readily and in larger numbers after sodium carbonate concentration than in direct smears or after sodium hydroxide concentration.

Five sputums, known to contain tubercle bacilli in small numbers, were divided into 4 equal portions after preparation of 2 direct smears from carefully selected particles of the crude sputum. One portion of each sputum was treated by 1 of the 4 following methods: Pottinger's dilution-flotation, antiformin digestion, Petroff's sodium hydroxide concentration, and the sodium carbonate concentration. Two smears of as nearly as possible the same size and thickness were made from each preparation and stained by the Ziehl-Neelsen method.

Greater numbers of bacilli were seen after concentration by the sodium carbonate method than after dilution and flotation. When the dilution method was used, clumping of bacilli was seen.

Can Sensitization Be Induced by Intracutaneous Injection of Tuberculin?—W. E. Nelson, A. G. Mitchell and E. W. Brown⁶⁸ tried to determine whether tuberculin in amounts as great

as or slightly greater than ordinarily used for skin testing is capable of inducing sensitization to itself in man. If this were the case, tuberculin testing after the initial injection would be valueless for the detection of tuberculous infection. The evidence does not support the theory of artificially induced tuberculin sensitization by single or repeated intracutaneous tuberculin injections for the following reasons:

1. The third injection was performed 96 hours after the first test, an interval presumably too short to permit induction of sensitization.

2. A consistent individual response was not obtained.

3. Neither were consistent maximal rates or sizes of reactions obtained in later tests.

4. X-ray evidence, usually accepted as diagnostic of tuberculous lesions, in children of all groups who had no or only questionably positive reactions in the first 2 tests, indicated that tuberculous lesions may be associated with a low degree of tuberculous allergy. This does not imply that sensitization to tuberculin or tuberculo-protein is impossible, but such sensitization does not appear likely from the ordinary use of tuberculin for purposes of cutaneous testing.

Intracutaneous Tuberculin Test of Mantoux: Method Employing a Single Injection—D. Anderson, and C. Harvey⁶⁹ devised a single injection technique for the Mantoux test, using purified protein derivative. This was employed in population surveys to detect a high percentage of the total positive reactors with a minimum of untoward reactions. They felt that a smaller injection ought to produce a correspondingly smaller allergic response in a susceptible subject as readily recognizable as that produced by the larger injection of the same strength. Accordingly, 123 volun-

teers, some known reactors and some clinic patients not previously tested, were given into the right arm an injection of 0.005 mg. of tuberculin purified protein derivative in 0.1 cc. of diluent, and into the left arm an injection of 0.00125 mg. of tuberculin purified protein derivative in 0.025 cc. of diluent. The 2 injections were given at the same time. It was found to be easy to measure the smaller dose with as much or almost as much accuracy as the larger dose. From this experiment it is concluded that an injection of one-fourth of the volume of the standard second strength injection of tuberculin purified protein derivative detects all or nearly all the reactors to the Mantoux test. The specificity of the smaller reactions is still unmistakable by the experienced interpreter. The sharper reactions are of substantially less severity. The scheme of dosage of Long, Aronson and Seibert should be followed when practicable, but if only 1 injection can be given this may safely and effectively consist of 0.00125 mg. of tuberculin purified protein derivative in 0.025 cc. of diluent. An experience of more than 1000 such injections has shown that, though sharp reactions are relatively frequent, they are practically never large enough to be inconvenient and that the proportion of reactors is as great as with the larger injection. Of the first 500 adult subjects tested with the single injection technic 33 had some degree of vesiculation, of these the reaction was large and more or less sore in 10 and in 5 some tenderness was complained of when the reaction was neither large nor vesicular. Only 4 subjects required treatment, 3 for blistering and 1 for itching.

Certain Anomalies of Tuberculin Reactions—O. Pasiseau, J. Valtis, and E. Kayem⁷⁰ point out that some investigators have called attention to the existence of negative cutaneous reactions in

children or adults who have been in close and prolonged contact with carriers of tubercle bacilli. Children living in prolonged contact with tuberculous parents reacted negatively to tuberculin tests, not only to cutaneous reactions but also to intradermal tests with 0.1 cc. of a 1:100 solution of tuberculin. In the course of the last 3 years, 17 cases of the type have demonstrated certain anomalies.

1 Long persistence of the dissociation between a negative cutaneous reaction to tuberculin and the positive intradermo-reaction to this substance;

2 Change of positive to negative cutaneous reactions.

It is indisputable that an organism which is free from tuberculosis never reacts to a cutaneous tuberculin test, but it cannot always be deduced from this that a negative cutaneous reaction is proof of the nonexistence of tuberculosis. Aside from that, there is a conclusion which has long been arrived at from the fact that a considerable proportion of subjects present a positive intradermal tuberculin reaction without a cutaneous reaction. It is necessary to consider the change from a negative cutaneous reaction as evidence of a primary tuberculous infection.

Old Tuberculin Diluted for Mantoux Test—R. Gottschall, and W. E. Bunney⁷¹ found that a diluent buffered to pH 7.2 with borax and boric acid, containing 0.04 per cent acacia and 0.5 per cent phenol, stabilized the tuberculins tested when diluted 1:10,000 and dispensed in rubber stoppered hard glass vials of 1 or 10 cc. capacity. This stability was proof against destruction by shaking for 7 days, exposure to indirect sunlight at room temperature for 4 months or prolonged transportation to warm climates and return.

Comparative Study of Tuberculin Patch Test and Mantoux Intracutaneous Test—H. Vollmer, and E. W. Goldberger⁷² tested 169 children with active tuberculosis. Only 1 of those who reacted positively to the Mantoux test with the stronger solution of purified protein derivative failed to react positively to the tuberculin patch test. Among 118 children admitted in a routine manner to the pediatric service of the Mount Sinai Hospital with various diseases the Mantoux test, even with 1 mg of old tuberculin, did not reveal a single case of tuberculous infection which was not already discovered by the tuberculin patch test.

Bronchography with Lipiodol in Pulmonary Tuberculosis and in Pulmonary Syphilis—A. Levi-Valensi, P. Sudaka, and R. Negri⁷³ did bronchographies with iodized oil, using a nasal tube on all, on 20 patients with various forms of pulmonary tuberculosis and 20 tuberculous patients with old syphilis. The instillation was found to be harmless. In 28 of the 40 patients treated, no reaction whatever resulted, whereas 12 exhibited an increase in temperature.

If the treatment is correctly carried out, it will practically always reveal an existing pulmonary cavity. The oil penetrated to the cavities in from 90 to 95 per cent of the 40 cases treated.

Bronchial dilatation is extremely frequent in the course of pulmonary tuberculosis. Pronounced bronchial dilatation was observed in 16 (80 per cent) of the 20 patients with various forms of pulmonary tuberculosis. It was observed in 60 per cent of the acute forms, in 75 per cent of the chronic fibrocaseous forms, and in 100 per cent of the ulcerofibrous and of the fibrous forms.

Bronchial dilatation was discovered in 17 of the 20 tuberculous patients with old syphilis.

Accidental Discovery of Symptomless, Nonmanifest Pulmonary Tuberculosis—C. H. Cocke⁷⁴ states pulmonary tuberculosis is so frequently uncovered by roentgenography that Cocke maintains that no physical examination is complete without its use. One of the most striking paradoxes of tuberculosis is the absence of parallelism between symptoms, signs and x-ray evidence of disease. It is common to find symptoms without demonstrable physical signs but with definite x-ray evidence. There may be absence of both symptoms and signs, and yet the roentgenogram may reveal sufficiently definite (active) disease to make the diagnosis clear. Again, though more rarely, the roentgenogram may seem apparently clear, though symptoms and signs are unequivocal. This type has a pathologic condition of such similar density to lung and other structures of the chest that it fails to register on the roentgenogram to the point of recognition. Of 10 cases cited only 1 patient admitted any appreciable loss of weight, only 1 complained of a cough, only 4 gave a history of temperature, only 1 gave a history of an attack of pleurisy, only 1 complained of increasing fatigue and mild digestive symptoms and only 1 at first reported sputum (but 6 were found to have acid rods in the sputum). With the possible exception of a young man who expectorated a little blood, there was no history in any of the patients which might seem to point expressly to tuberculosis. The roentgenogram, however, in every instance was definitely positive for tuberculosis, 4 cases presenting definite cavitation not demonstrable by physical examination.

Differential Diagnosis

Hodgkin's Disease and Tuberculosis—C. Mulky⁷⁵ states that Hodgkin's disease is manifested by progressive en-

largement of the lymph nodes, clinically resembles glandular tuberculosis and is often confused with it

It is important to make a diagnosis as early in the disease as possible, as glandular tuberculosis is comparatively mild and usually is curable while Hodgkin's disease invariably terminates fatally within 2 to 5 years despite any form of treatment yet discovered.

When groups of internal lymph nodes, such as the tracheobronchial or retroperitoneal glands, are involved before any external enlargements are noted, diagnosis is difficult and a definite diagnosis cannot be made except by histological examination of an affected gland.

When Hodgkin's disease involves the retroperitoneal glands, it closely simulates tuberculous peritonitis. It gives rise to abdominal pain and tenderness, digestive disturbances, and frequently jaundice or ascites.

Hodgkin's disease occurs in the same age group as tuberculosis; namely, in early adult life. There is the same insidious onset of such symptoms as loss of weight, fatigue, low grade fever, secondary anemia, cough, dyspnea, pleural effusion, hoarseness or even complete loss of voice due to pressure on the recurrent laryngeal nerve.

Physical examination will not reveal any abnormality unless there is pleural effusion or massive enlargement of the mediastinal glands. There may be displacement of the heart from pressure. The spinal and parasternal areas of dullness may be widened and there may be some râles due to an associated bronchitis.

X-ray examination shows an irregular mass in the mediastinum which may be obscured by the heart shadow unless viewed obliquely. When scattered bronchial nodes are involved, there are patches of infiltration throughout the lung areas.

Tuberculosis and Hodgkin's disease may occur in the same person at the same time. Sometimes patients having Hodgkin's disease develop pulmonary tuberculosis with positive sputum as a terminal stage.

The blood picture varies with the severity and stage of the Hodgkin's disease. There is a secondary anemia which in the later stages may become extreme. The number of white cells may be within normal limits in the early stage but later there may be marked leukocytosis. The differential count is variable, but an increase in the number of eosinophils is significant.

PROPHYLAXIS OF TUBERCULOSIS

New Observations on Infants Having Received BCG by Mouth and Living in a Contaminated Milieu—

H. Stevenin, S. Levi and J. de Prat¹⁶ report observations on 81 children who had been given BCG by mouth and who remained in a tuberculous milieu. Although these children were not isolated, their tuberculous morbidity was below that of the nonvaccinated children, their mortality from tuberculosis was *nil* and the cutaneous reaction with tuberculin was more often negative in the children treated with BCG than in those who were not so treated. These observations were made simultaneously in 2 different dispensaries and they are in perfect concordance with those made in 1930. Not the slightest danger is involved in the administration of BCG to the children by the oral method, even when it is impossible to take all the precautions which are necessitated by this method of prophylaxis against tuberculosis.

Immunization Against Tuberculosis—Study of Essential Factors—M. I. Levine, P. Vogel and H. A. Rosen-

berg⁷⁷ report on the efficacy of B C G vaccination against tuberculosis in New York City for 12 years up to April 1, 1937. During this time, 1830 children of tuberculous families were followed. Of them, 880 were vaccinated and 950 served as controls

At the outset of the study an attempt was made to control the experiment by dividing the children into 2 equal groups, those vaccinated and those not vaccinated. This procedure was followed from 1926 to January 1, 1933. In all, 955 children were studied, 435 of whom were vaccinated, when the procedure of selection was changed so that alternate children were vaccinated and the others served as controls. Under this selection, 744 children were observed from January 1, 1933 to September 1, 1936, 383 being vaccinated and 361 held as controls. The results of B C G vaccination before alternate selection was 16 deaths in the control and 3 deaths in the vaccinated group. The results of B C G vaccination after alternate selection was instituted were 4 deaths in the control and 6 in the vaccinated group. The manner of selecting cases for vaccination or as controls exerted a marked influence on the final results obtained

TREATMENT OF TUBERCULOSIS

Psychology of the Tuberculous Patient- F. M. Pottenger⁷⁸ states that the object of treatment is not to heal the tuberculosis alone, but to heal the patient who has it, and fit him to live a happy life, able to produce to the best of his physical ability

The physical effect of tuberculosis is injury and destruction of local body structures and alteration of body functions. A disturbed body function causes worry, fear, anxiety, and depression, and

can alter the personality of a patient, creating new departures from the normal, according to the state of his physical body. Likewise the structure of his body and body functions may be changed by varying psychological states. The composite physical and physical being shows many variants and that reaction to disease or any other stimulus is individual. The general effect of tuberculous disease on the body and likewise upon the psychical aspects of the individual will vary according to its extent and severity.

The earlier the case is diagnosed the less the psychological upset, as the earlier the disease, the minimum of ill feeling and the shorter the period of treatment, during which time there is an enforced physical and mental inactivity and the patient is prone to mental and psychological deterioration.

It is important for the physician sympathetically and wisely to counsel the patient as to the hopefulness of prompt proper treatment and to repair his psychological injuries as well as his physical ones during the course of treatment, by directing the patient's mental state and development as much as is consistent with his progress. It must be kept in mind that thoughts, wishes, hopes, joy, happiness, sorrow, disappointment, discouragement, and despair are emotions that react favorably or unfavorably on a patient's progress toward recovery.

During the course of treatment, it is necessary for the doctor to direct the patient to healthful thinking and living so he may take his place in life, enjoying and producing to the best of his physical ability. As the patient's health improves, he should be encouraged to gradually start doing things that will develop his powers of concentration and correlation

and acquaint him with his powers of exertion.

This type of program relieves the patient of that awful defeatism which one has when one has not had the proper psychical aid and the proper physical rehabilitation. It shortens the time of treatment, for it relieves the patient of depressive and harmful emotions which hamper physiologic function. It preserves independence, self-respect, ambition and fitness.

Rehabilitation and finding of suitable work for patients who are able to resume work but unable to resume their former working obligations is important, rather than waiting longer until able to resume their former work, as there is the risk of further deterioration as long as they are able to work and are unemployed.

Carbon Dioxide Inhalation—A. L. Banyar⁷⁹ states that in cases of pulmonary tuberculosis where numerous moist râles or the presence of widespread rhonchi are indicative of the formation and retention of mucopurulent inflammatory products an *adequate drainage of the lung* is necessary, as accumulation and retention of viscid, tenacious secretions in the bronchial tract are likely to cause excessive cough and massive or patchy atelectasis.

The inhalation of a mixture of *10 per cent carbon dioxide* and *90 per cent oxygen* is a safe and efficient method for the treatment of dyspnea and atelectasis, and for the management of cough in pulmonary tuberculosis. It is conducive to a liquefaction of bronchial secretions and to their efficient removal by means of the increased respiratory motion of the lung, by the blanching of the bronchial mucous membranes, and by the increased peristalsis of the bronchial tubes.

The *evacuation of the bronchial tract* is likely to be followed by the

opening up of previously atelectatic areas and consequently by the disappearance of dyspnea and cyanosis.

Prontosil in Experimental Tuberculosis—H. F. Dietrich⁸⁰ chose the disodium salt of 4 sulfamido-phenyl-2'-azo-7'-acetylamino-1'-hydroxynaphthalene-3,6'-disulfonic acid (prontosil) in a 2.5 per cent solution for its effect on experimental tuberculosis in the guinea pig. Six animals were given 0.5 cc of a suspension of tubercle bacilli recovered from the lung of a patient dying of tuberculosis and 4 were injected with 0.25 cc of the suspension. All inoculations were made subcutaneously just cephalad to the right groin. The *prontosil* administered was injected into the peritoneal cavity in single daily doses of 100 mg per kg of body weight. No animal showed any peritoneal reaction to the injected prontosil. Treated animals died much sooner than did the untreated controls. The pathology of tuberculosis offers an excellent reason why, even if one possessed an agent strongly bactericidal for the tubercle bacillus *in vitro*, the bacilli might be unaffected in experimental and clinical infections. Prontosil did not inhibit the growth or spread of tuberculosis bacilli, even though it came in contact (by prontosil being given before inoculation with tubercle bacilli) with them before they were fixed in the tissues.

Results of Collapse Therapy in Children—M. Siegal and B. Singer⁸¹ between the years 1928 and 1936 performed *artificial pneumothorax* on 105 children from 5 to 15 years of age with open pulmonary tuberculosis. The sputum of all these children contained tubercle bacilli, and a cavity was visible in the roentgenogram in 95 per cent of the cases. The predominant clinical types seemed to have begun either as isolated infiltrative tuberculosis, usually in the

infraclavicular region with a tendency to cavitation and bronchogenic dissemination, or as bilateral disseminated tuberculosis, apparently the sequela of a benign hematogenous seeding, with a tendency to the formation of nodular-cirrhotic productive lesions with or without small cavities. In addition, there were far advanced bilateral forms, usually with bilateral cavities. Forty children improved, 33 remained unimproved and 32 died. Conversion to negative sputum was obtained by means of pneumothorax alone in 21 of 28 children within 3 months and in all 28 children within 6 months after the start of collapse therapy. Moderate or large amounts of pleural effusion developed in the course of pneumothorax in 28 cases. Tubercle bacilli alone were found in 9 cases, pyogenic organisms and tubercle bacilli in 4 cases and pneumococci in 1 case. The fluid was resorbed in only 2 of the 13 cases in which either tuberculous or mixed infections were present. After collapse therapy, 60 per cent of the patients with isolated infiltrative tuberculosis (unilateral) improved. Of those with infiltrative tuberculosis (with contralateral spread) 22 per cent improved and 29 per cent of those with disseminated tuberculosis improved. With a small amount of collapse (less than 50 per cent) 15 per cent of the patients improved, with a moderate amount (from 50 to 75 per cent) 30 per cent improved and with a large amount (over 75 per cent) 50 per cent improved. The best results were obtained among the children with unilateral isolated infiltrative tuberculosis in whom a large amount of collapse could be obtained. Regression of the contralateral process was seen in only 12 per cent of the cases in which bilateral lesions were treated on 1 side only, while progression occurred in 53 per cent of these cases. Unilateral collapse therapy is inadequate in such cases

and collapse on both sides is required. By means of bilateral collapse therapy the number of improved children increased. Internal pneumolysis, in patients with broad, extensive adhesions, was rarely successful and was attended with considerable danger. Several children improved after thoracoplasty. Most of the deaths among the treated children occurred within the first 2 years after the initiation of therapy, after which relatively few children died. Most of the deaths were due to the progression of the disease on the contralateral side or because the process was too far advanced at the start of therapy. Of 87 untreated children with open lesions admitted to the hospital between 1929 and 1936 and observed to date, 95.4 per cent died, 1.1 per cent are unimproved and 3.4 per cent are improved.

Positive Intrapleural Pressure as an Aid to Pneumothorax Therapy—

G. Edsall^{1,2} states since no detailed studies on positive pressure were to be found in the literature, Edsall made an analysis of the pneumothorax treatments administered at Trudeau Sanatorium during the years 1929 to 1933, inclusive. From a total of about 275 patients receiving pneumothorax, 68 were found in whom, at some time during their stay, intrapleural pressures above zero on inspiration had been recorded. All cases were considered in which the pressure had remained positive throughout the respiratory cycle for more than occasional refills. Of the 68 cases, 43 remained in which positive pressures were induced to a significant degree and sustained over several refills, but in only 30 of the cases were there data adequate for comparing the effects of normal versus positive pressure. In these 30 cases the treatment was applied after a control period on normal pressure. Positive pressure was usually employed to improve a

collapse rendered inadequate under normal pressures because of pleural adhesions. In 15 cases positive pressure produced an increase in collapse of more than 15 per cent; the average increase in the 30 cases was 17 per cent. The increase obtained was not consistently related to the pressure employed. In 13 cases, healing of cavities under both types of pressure could be compared. Ten cases showed accelerated healing while under positive pressure. In 17 cases with previously unimproved Gaffky counts, induction of positive pressure was followed within 2 months by a negative sputum in 2 cases and a lowered Gaffky count in 7 other cases. General results following positive pressure were definitely good in 14 of the 30 cases and possibly beneficial in 7 others. Complications possibly related to the use of positive pressure occurred in 4 cases. In the 13 cases in which the effects of pressure were not comparable, 2 major complications occurred subsequent to the induction of positive pressure. The judicious and careful application of moderate positive pressure is a worthwhile procedure in selected cases in which simple pneumothorax has failed to produce satisfactory collapse and healing of the lung.

Pneumoperitoneum, Oxyperitoneum, and Nitroperitoneum in the Treatment of Pulmonary and Abdominal Tuberculosis—F. W. Burges^{8,9} reports that *artificial pneumoperitoneum*, which is inflation of the peritoneal cavity by the injection of gas, has been in use since 1908. The treatment is of value in all cases of tuberculosis of the mesentery, peritoneum, and intestine. It should be used, in addition to pneumothorax, in those tuberculous cases having vomiting attacks, extreme repugnance to food, or unexplained chronic abdominal pain. The procedure is harmless in the hands of the trained pneumo-

thorax operator, it is painless, and leaves no scar. It will not increase dyspnea and is effective in advanced bilateral pulmonary tuberculosis in which all functioning lung is needed. Pneumoperitoneum should be tried in tuberculosis of the lungs in any case where pneumothorax is indicated but impossible or ineffectual due to irremovable pleural adhesions, before resorting to more radical treatment such as thoracoplasty.

The gases in use are *oxygen* in which case the term oxyperitoneum applies, *nitrogen* resulting in nitroperitoneum, or *air* for pneumoperitoneum. Oxygen is advised for the initial induction and for the first few refills as oxygen is rapidly absorbed by the tissues should any gas fail to be placed or retained in the peritoneal cavity. Oxygen seems to be more therapeutically effective in the treatment of tuberculous enterocolitis and tuberculous peritonitis. The objection to it is that due to its rapid absorption from the peritoneal cavity, refills must be given as often as twice weekly. Air is not absorbed as rapidly as the oxygen and refills need be given only once weekly, but air does not seem as active therapeutically as oxygen. Nitrogen is used as soon as there is freedom from adhesions and a free space in the peritoneal cavity in which to insert the needle. It is used in those cases in which the local effect of the oxygen in the peritoneal cavity is not needed, but where the sole need is elevation of the diaphragm. Nitrogen refills need be given only at 2-week intervals.

The technic is as follows:

The patient lies on his back with abdomen and lower chest exposed. The skin in the operative area is sterilized with untinted tincture of metaphen or untinted tincture mercressin. A point just below the rib margin in the left nipple

line, or a point $1\frac{1}{2}$ inches to the left of the umbilicus, is selected.

With strictly aseptic technic, the skin and subcutaneous tissue is anesthetized with an injection of $\frac{1}{2}$ dram (2 cc.) of $\frac{1}{2}$ per cent sterile novocain solution, using a 27 gauge needle. Then a $2\frac{1}{4}$ inch, 19 gauge rustless steel needle attached to a 5 cc. syringe of $\frac{1}{2}$ per cent sterile novocain solution and to the gas line from the pneumothorax apparatus by means of a 3-way stopcock, is inserted into the anesthetized spot, slowly advancing the needle, and endeavoring to anesthetize ahead of the point by frequent small injections of novocain from the attached syringe. This proceeds down to and through the peritoneum, which can be identified when encountered by the needle point by the experienced pneumothorax operator. The valve of the stopcock is then turned, disconnecting the syringe and connecting the needle with the gas line from the pneumothorax apparatus, and oxygen is allowed to flow.

The amount of gas injected depends upon the pressure caused by the introduction of the gas, which is measured on the manometer tube of the apparatus, and also upon the feeling of fullness experienced by the patient. Pressure should not go above plus 4 centimeters of water at the first injection, with increase of pressure of 1 centimeter of water at succeeding refills up to 10 or 12.

The procedure should be entirely painless, but there may be slight discomfort between the shoulders immediately after the initial and first few refills, due to raising of the diaphragm. No dressing should be applied after withdrawal of the needle.

This procedure raises the diaphragm bilaterally and frees it from the dead weight of the liver, stomach and spleen, thus increasing the expulsive motility of the diaphragm under cough. This re-

sults in increased ease and diminished effort in raising sputum and clearing the bronchial passages.

Pneumoperitoneum has the following advantages over phrenic crush or exeresis:

1. There is not the surgical risk nor resulting morbidity.

2. Gastric symptoms are alleviated by pneumoperitoneum while after left-sided phrenic interruption the gastric difficulties are often severe and persistent.

3. Pneumoperitoneum can be abandoned at will, whereas phrenic interruption persists for at least 6 months.

4. Phrenic interruption interferes with the cough impulse, the lower lobe becomes a cesspool of stagnant secretions, and the result is pulmonary interstitial fibrosis and bronchiectasis, and, if the patient hemorrhages, there is danger of the patient drowning in the blood, or at least of a septic pneumonia.

Induced Pneumoperitoneum in Treatment of Pulmonary Tuberculosis—E. S. Bennett⁵⁴

during the last 2 years has induced pneumoperitoneum in 200 patients. Thirty-two of these patients have died since, after an average of about 8 months of treatment. Necropsies were performed on 15. In view of the advanced stage of the disease in most of these patients this case fatality rate cannot condemn pneumoperitoneum, especially since the necropsies did not indicate that this was a factor responsible for death in any case but 1, in which instance it accelerated what was otherwise an apparently certain death. Clinically and symptomatically, improvement was noted in more than half of the patients treated. A careful analysis was made of the cavities in 120 of these cases; 90 per cent showed cavitation with a total of 211 cavities. Of the 211 cavities, 22 per cent of those in the upper third, 33 per cent of those in the middle third and 31 per cent of those in the lower

third could not be visualized roentgenologically after pneumoperitoneum had been well established. Reduction in the size of cavities was noted in an additional 12 per cent of those in the middle third. The remainder of the cavities showed no change or became larger, or more recent roentgenograms were not available because of the short duration of the treatment or the departure of the patients. In 11 patients showing infiltrative lesions without cavitation, 4 showed marked clearing of infiltration under pneumoperitoneum. Fifteen of the 200 patients after a period of artificial pneumoperitoneum underwent thoracoplasty or extrapleural pneumothorax who previous to the addition of pneumoperitoneum were in too poor condition or had too much contralateral disease to withstand these more radical operations. Pneumoperitoneum did not prove particularly effective when used in an emergency to control hemorrhage. A change from a previously positive to a negative sputum, following the establishment of pneumoperitoneum, occurred in 57 patients out of the 173 whose sputum had been positive prior to the institution of this form of treatment, representing a conversion of more than 30 per cent.

Influence of Pneumoperitoneum on Electrocardiogram—A. Agnello⁸⁵ observed the behavior of the electrocardiogram before and after establishment of pneumoperitoneum in 20 patients suffering from tuberculosis. Collapse treatment especially by artificial pneumothorax, was already established in the majority of the cases. The electrocardiograms were taken of patients at rest and during fasting, immediately before and after an insufflation of about 300 cc of oxygen into the peritoneal cavity. Pneumoperitoneum induced an increase of the pause between 2 consecutive cardiac revolutions (atrioventricular complexes), as

shown by the prolongation of the T P space in the electrocardiogram and also alterations of the R, S and T waves in the 3 leads. The electrocardiographic alterations are due to deviations of the electrical axis from displacement of the heart and also to functional changes of the heart from vagosympathetic stimulation. The functions of the heart are good in pulmonary tuberculosis before and after establishment of collapse of the lung and of pneumoperitoneum. The latter has both a mechanical action and a capacity of stimulating the sympathetic nervous system.

An Appeal for Conservatism in Phrenic Nerve Surgery—E. E. Carpenter⁸⁶ states that phrenic nerve surgery paralyzes the diaphragm, attacking one of the main motivating forces of the respiratory mechanism, and the results are unpredictable.

Diaphragmatic paralysis gives marked relaxation in the lung above and a lung contracting or that has contracted as far as it can while healing will receive a new impetus in the process of this contraction.

Many cavities actually are held open by the pull of the thoracic walls *via* the intervening elastic tissue of the lung, by relaxing the whole tension of the lung by diaphragmatic paralysis such cavities will tend to close due to the inherent elasticity of the organ. Apical cavities that are not subpleural are commonly known to close after a successful rise of the diaphragm is accomplished.

If a paralyzed diaphragm will assist in healing a fibroexudative process, even though it does not close an apical cavity if present, the phrenic nerve interruption has been of value since apical surgery can be performed to take care of the cavity.

Beneficial results may be expected when diaphragmatic paralysis is done under a lung:

1. Which is contracting;
2. Which has contracted as far as it can;
3. Containing cavities moderate in size, not subpleural;
4. Where cavities show a tendency to close;
5. Presenting disseminated fibroexudative lesions, especially in the lower two-thirds;
6. To diminish the intrathoracic cavity following pneumothorax where too great or too rapid re-expansion might enhance the reopening of a former large cavity;
7. As an adjunct to pneumoperitoneum;
8. As an adjunct to pneumothorax when apical (or upper chest) adhesions not amenable to cutting exist and prevent a cavity from closing (the lung being firmly attached to the diaphragm)—the relaxation acquired will often allow such a cavity to close.

Phrenic interruption is contraindicated in the following conditions: Enormous cavities; moderate sized cavities which are subpleural, cavities situated among the large branches of the bronchi, cavities with heavy walls, or those with a great deal of infiltration about them.

Phrenic nerve surgery is not a simple, harmless procedure. Berry, in 1930, established a mortality rate of $\frac{1}{2}$ per cent in a review of nearly 5000 cases. Some of the deaths have been due to hemorrhage following exeresis.

The phrenic nerve should never be permanently interrupted until a temporary procedure has been executed, then after regeneration has occurred deciding whether the next step should be: Nothing, rephraxis, or severance. It may be advisable to crush the phrenic nerve 2 or 3 times, allowing an interval between each phraxis to re-establish muscular tone of the diaphragm.

In phrenic nerve procedures, as in all chest surgery, an attempt should be made to preserve all the breathing space consistent with efficient and sufficient compression, and to interfere as little as possible with the mechanism of the breathing apparatus. This does not mean that adequate surgery should not be done.

If no undesirable side effects are noted it is a simple matter to obtain permanent interruption by resecting a centimeter of the main trunk which has regenerated. If an ultimately movable diaphragm is considered essential, phraxis can be done again.

Objections have been raised to phrenic nerve phraxis or severing and suture because of the frequent failure to obtain complete paralysis of the diaphragm when these operations are done. These failures are the result of unsevered branches which arise from the cervical plexus to join the main branch of the nerve. The search for these accessory or "neben" branches complicates the operation, but the time and effort thus expended may often pay the surgeon good dividends in the end. The above objection can be obviated by stimulating the nerve trunks and branches during operation with an electric current derived from a generator such as is used in physiology classes in the study of nerve reactions. (A suitable electrode can be made with 2 fine knitting needles placed parallel about $\frac{1}{4}$ inch apart and moulded into a handle of dental vulcamate, shaped to the desire of the operator and after being vulcanized the whole is boilable.

The procedure is accomplished by attaining the fascia of the anterior scalenus muscle in the usual manner and isolating the main branch of the nerve which is stimulated for identification. If the phrenic nerve is stimulated, the diaphragm will forcefully contract, which

action can be felt by the patient as a hiccough and by the surgeon as an impulse in the upper abdomen on the operated side.

Following the fascial plane laterally, the trunks of the fourth, fifth or (occasionally) sixth cervical nerves are carefully approached and stimulated, especially observing the fifth, which so often gives rise to a branch either to the main trunk, or may exist as a separate nerve, the latter occasion being uncommon. When this is done, the arm will jerk, but if there be an accompanying branch, the diaphragm will also react. The signal thus being given that there is a branch to the phrenic nerve in the main trunk of the fifth (or other trunk) it is to be inspected, the *neben* branch found and stimulated on its own isolated substance. There should now be a contraction of the diaphragm, but little or none of the muscles of the arm.

The branch may run within the sheath of the larger nerve (again especially true of the fifth cervical) for some distance and can be seen as a ridge upon the main nerve. It can be easily isolated and removed from the sheath of the larger trunk. The branch can now be identified as above and disposed of as is seen fit. If it is small, it is probably as well to resect a segment of it, as sufficient diaphragmatic contraction will be given by the main trunk on regeneration, and this procedure obviates the necessity of search for the elusive branch at reoperation. If large, it can be treated as the main trunk (described below) and crushed at reoperation. Any small nerve branches running diagonally across or parallel to the anterior scalenus muscle should be stimulated and identified in the same manner.

The fascial plane is then followed medially, where any nerve running downward (being sure not to be too near the carotid

sheath or region of the vagus) can be safely stimulated and, if diaphragmatic response occurs, this branch too can be dealt with. When found, diagonally or medially situated branches usually come from the third cervical. No strand of fascia or tissue resembling nerve trunks are severed or injured in any way unless there is diaphragmatic response to stimulation. Once the main trunk is isolated and small branches severed, a strand of No. 7 or 9 twisted black silk is tied loosely around the nerve. After leaving the thread sufficiently loose to insure no undue tension, the distal end is embedded in a suture coaptating the fibers of the platysma. This silk thread serves as a guide back to the nerve at reoperation.

After infiltrating with novocaine, the nerve is now crushed carefully in a hemostat from which the serrations have been filed and whose smooth surfaces approximate evenly and accurately (tested with dental articulating paper) because failure of regeneration has been known following phraxis by the ordinary hemostat as histologic severance often takes place due to the serrations acting on each other in a scissors-like manner.

When there is contralateral pneumothorax or other condition in which the diaphragmatic paralysis may cause an undue dyspnea, a trial nerve interruption can be accomplished by injecting the main trunk (the branches having been disposed of) with $\frac{1}{4}$ to $\frac{1}{2}$ per cent quinine and urea hydrochloride at low pressure, which procedure will bring about a paralysis of from 36 to 72 hours, which interval will give the hemidiaphragm time to rise somewhat into the chest. The procedure will present an approximate idea of what can be expected following lengthier paralysis. If no dyspnea is encountered, the black silk thread can then be followed back to the phrenic nerve with facility and the latter crushed.

If dyspnea results, nothing further is done except to obtain more perfect skin coaptation, if this has not been accomplished. If only restraint of diaphragmatic motion for pulmonary rest is desired, and little or no rise is wished (fearing possible coalescence of multiple small cavities, dyspnea, etc.) the main trunk can be split longitudinally leaving a fraction of the nerve intact, and the remainder crushed. A very small segment will prevent diaphragmatic rise.

In all cases, immediate fluoroscopy is advised before skin closure and usual signs of diaphragmatic paralysis observed, remembering that too free use of novocain in the region of small nerve trunks or branches will cause temporary blocking of unsevered branches, and their recognition thus made difficult. If there is still movement, the search for branches is recommended.

Thoracoplasty—End Results—L. S. Peters and P. G. Cornish⁸⁷ were able to trace only 78 patients out of more than 300 who had thoracoplastic operations.

On 40 patients, complete thoracoplasties were performed. Twenty-one per cent of them became well with negative sputum and closed cavity, while 54 per cent are dead. All these patients were hopelessly ill and would ultimately have died had it not been for the surgical intervention. None was able to work even part time. The other 25 per cent are living with positive sputum and open cavity, no better than before operation and will ultimately die of tuberculosis.

On 38 patients a partial thoracoplasty was done. Of them, 50 per cent are well with negative sputum and closed cavity, while 34 per cent are dead. The other 16 per cent still have positive sputum and open cavity and are unable to work. Undoubtedly they will die of tuberculosis, but had thoracoplasty not

been done, all would have died of their disease.

The indications for thoracoplasty are about the same as for pneumothorax. The end results prove that all patients who must otherwise die of their tuberculosis should be given the benefit of thoracoplasty if they offer a fighting chance for recovery.

All the cases reported as well have been so for from 2 to 15 years.

The Lung Volume After Thoracoplasty—J. S. Harter, R. H. Overholt, H. J. Perkin⁸⁸ report preoperative and postoperative determinations of the volume of the lung made in 32 patients who were subjected to thoracoplasty as a part of the treatment of pulmonary tuberculosis. The method of Christie was used. For this study, only patients in whom thoracoplasty was the sole form of collapse therapy at the time of the last determination were included. The time interval between the last operation and the postoperative determination varied from 4 to 18 months. The condition of all patients was classified as apparently arrested, and all patients were ambulatory or working.

Eight patients showed a greater lung volume after thoracoplasty, the percentage change varying from plus 1 to plus 50. Twenty-four patients showed a reduction in the postoperative lung volume, the percentage change ranging between minus 5 and minus 50. The average preoperative value for all patients was $2\frac{2}{3}$ liter and the postoperative value was 1.8 liters, the difference being 0.5 liter, with a standard deviation of plus or minus 0.22.

The clinical impression drawn from a series of 179 patients in whom far advanced disease had been arrested by thoracoplasty, and from 121 of these patients who were working, was that the great majority of patients rehabilitated

by thoracoplasty do very well in respect to pulmonary function. Relatively few of the patients complain of dyspnea on exertion, or show other effects of pulmonary deficiency, while a few, who had symptoms, such as tightness of the chest, wheezing, or dyspnea on slight exertion, have been relieved by selective thoracoplasty.

The readjustment of the size of the thoracic cage to the size of the healthy lung, the relaxation of distorted pulmonary tissue, the dropping of the hilus, and the return of the lower lobe to its normal limits may increase the patient's ability to use the remaining uninvolved lung.

Appraisal of Closed Internal Pneumonolysis in Pulmonary Tuberculosis—*Relation of Tuberculous Empyema to Operation*—E. C. Drash⁸⁹ reports on 251 separate pneumonolyses performed on 230 patients, performed by the high frequency current and the Davidson thoracoscope. Most of the patients were receiving pneumothorax refills for from 4 to 6 months or longer. The only valid contraindication to pneumonolysis is the existence of an acute pleurisy with fluid, either serous or purulent. Successful operations can be done in chronic afebrile cases of pleurisy with effusion, provided the adhesions are not covered with fibrin and can be clearly seen. The general results, exclusive of complications, have been most satisfactory. There have been no deaths attributable to the operation. Of the cavities present, 74.8 per cent were closed. A satisfactory collapse was obtained in 86.4 per cent of the patients operated on. Sixty-four patients (27 per cent) had fluid in the pleura at the time of operation. Fourteen additional patients (6 per cent) had fluid after operation, mostly within a few days. Among the total of 78 patients (33.6 per cent)

who had fluid at one time or another, in 6 the fluid became purulent. The total incidence of clear fluid and of tuberculous empyema in the present series is well within the limits of corresponding incidence to be expected from pneumothorax alone. Therefore, the evidence indicates that pneumonolysis is not an important factor in the development of intrapleural fluid. Only 1 patient had tuberculous empyema within less than 5 months after operation. Five (of 99 operated on) of the 6 patients with tuberculous empyema came from 1 institution which has a high proportion of patients with moderate and far advanced pulmonary tuberculosis. Rupture of a cavity into the pleura occurred in 3 of these, followed immediately by death. As they occurred 3½, 4½ and 9 months after operation, they were not ascribed to it.

Extrapleural Pneumothorax—*Technic, Indications, and Maintenance of*—O. Monod⁹⁰ states that extrapleural pneumothorax is the highest expression of surgical apicolysis. Any therapy of pulmonary collapse employed in lesions involving the upper pulmonary lobes aims to free the apices. An apicolysis has been produced in several ways, the commonest methods being scalenotomy, first rib resection and thoracoplasty.

An extrapleural pneumothorax may be obtained by the posterior route, resection of the fourth rib, or by the anterior route, resection of the second rib. The costal resection embracing a segment of from 8 to 10 cm. is sufficient to permit all the necessary surgical manipulations.

The posterior route is more frequently employed because the majority of the lesions are located centrally and posteriorly. Furthermore, closure is more easily accomplished. The anterior route should be chosen in the presence of a

cavity which is located near the anterior costal arches.

The patient is operated upon in the sitting position and local anesthesia with novocain (1:200) is employed. The advantages are (a) free cough and expectoration, and (b) better observation of the physiological reactions especially during the mediastinal detachment.

A rectilinear incision is made downward and outward extending from the spinous process of the second thoracic vertebra, 4 cm. below the vertebra prominens, to the internal border of the scapula, about 2 or 3 cm. below its spine. This incision reaches exactly the fourth rib.

The trapezius muscle is incised externally and divided internally. The rhomboideus muscle is divided and the serratus superior posterior is disinserted. It is necessary to avoid injury only to the spinal nerve which descends along the internal border of the scapula.

A costal resection is subsequently performed. The fourth rib is resected over a segment of at least 8 cm., preferably from 10 to 12 cm. The periosteum is saved for about 1 cm. beyond the osseous stumps on either side. This is necessary in order to obtain a proper closure.

The pulmonary apex is then freed by inserting a finger and a suitable pleural detacher between the costal wall and the parietal pleura. This manipulation should be performed cautiously because if done too rapidly it may cause an intense nervous shock. All the faces must be detached. As the plane of cleavage is more difficult to find on the mediastinal side and, also, because of the frequent presence of adhesions, detachment in this region is fraught with considerable difficulties.

In general, adhesions due to peripleuritis are solid and difficult to break and in some cases the line of cleavage

cannot be found. The adhesions should not be broken forcibly because this may lead to hemorrhage, perforation, and suppuration.

The wound is closed in layers without drainage. If the anterior route is chosen, the pectoralis major muscle is divided and a segment of the second rib, including its cartilage, from 10 to 12 cm. long, is resected. Special attention should be given in order that injury to the internal mammary vessels be avoided.

In every case the detached area should be sufficiently extensive, reaching from the pulmonary apex downward to a point well past the principal lesion.

In order to maintain an artificial extrapleural pneumothorax, it is necessary to observe fluoroscopically the extent of the extrapleural pocket. Usually during the first few days following the intervention, the extrapleural pocket descends spontaneously to the level of the ninth rib or even to the diaphragm, which produces a total pneumothorax of the pleural cavity, and indicates an extensive pulmonary collapse.

The injection of 10 cc. of lipiodol into the pocket will give a better fluoroscopic visualization.

If the extrapleural pressure is too high, a puncture should be made to remove air or fluid. If the pressure is too low, lipiodol and air should be injected (usually from 50 to 75 cc.) to bring the pressure up to zero. During the first few postoperative days, positive pressures should be avoided to prevent emphysema.

The usual complications are

1. Insufficient or excessive pressure within the extrapleural pocket.
2. Emphysema.
3. Hemorrhage into the pocket;
4. Perforation of the cavity, either accidental or postoperative;

5. Suppuration ;
6. Focal reactions

The above procedure was used on 40 patients and showed that the immediate results are usually good and the patient's general condition rapidly improves. Expectoration subsides and sputum specimens are free from mycobacterium tuberculosis. The results closely resemble those obtained from an artificial intrapleural pneumothorax.

Its Use in Treatment of Pulmonary Tuberculosis—Preliminary Report—R. H. Overholt and O. S. Tubbs⁹¹ up until the present time selected for extrapleural pneumothorax only those patients for whom no other form of collapse therapy offered any hope of a successful outcome. Extrapleural pneumothorax is not introduced to replace the modern selective thoracoplasty but is an alternative measure when the latter is contraindicated. The factors which render the patient with pulmonary tuberculosis unsuitable for thoracoplasty are evidence of too great activity, extensive bilateral lesions of a fibrocavernous nature and complicating factors (insufficient cardiovascular reserve, generalized emphysema, asthma, and the like).

The operation has been performed 31 times (in 28 patients) under cyclopropane and oxygen inhalation anesthesia or a combination of local infiltration with paravertebral block of the upper intercostal nerves, 1 per cent procaine hydrochloride being used.

On return to the ward, an oxygen tent has rarely been needed even in the bad risk patients. Intravenous infusion has been used if the blood pressure fell below 100 systolic, so that the patient may sit up soon after operation. All the patients had more or less interstitial emphysema during the first 24 hours, but in no case has it caused any distress other than slight tenderness of the

affected tissues. Sputum was not retained for more than 36 hours. Following extrapleural pneumothorax, patients are able to expectorate more efficiently and sooner than after thoracoplasty.

The frequency and amount of air refills to maintain the space so as to give the desired selective collapse have been controlled by frequent roentgenograms, fluoroscopy and consideration of the manometric pressure.

In 3 cases almost the whole space became filled with blood clots which could not be aspirated through a needle. Infection in the extrapleural space developed in 4 patients. In 3 of these there is definite evidence of a bronchial fistula. In another case evidence is lacking, although it is possible that the lateral wall of the cavity became necrotic because of its separation from the wall of the chest. Regardless of this complication, the patient has improved sufficiently to consider thoracoplasty. Most of the patients will eventually require conversion of the extrapleural pneumothorax to the permanent collapse of thoracoplasty, because of the extensive disease present in those selected for this form of treatment. Should the operation eventually be applied more widely to include young patients with less extensive disease, the ultimate fate of the space would be subject to the same rules that apply to an intrapleural pneumothorax.

Extrafascial Apicolysis (Semb)—J. W. Gale and P. A. Midelfart,⁹² in January, 1936, began to use the extrafascial apicolysis of Semb, because of failures in attempting to collapse certain apical, rigid-walled cavities by means of the usual thoracoplastic procedures.

The following technic was used on 65 primary cases and 8 revision operations.

The first rib is resected entirely before dividing the anterior scalenus muscle above the periosteum, as this is a

safer and easier method. The extrafascial separation is started from the apex, as a rule, but when a peripleuritis makes this difficult it is started at the level of the third or fourth transverse process and carried upward. The extent of the apicolysis is determined by the preoperative condition of the patient, the location and nature of the underlying pathology, the amount of paradoxical breathing, the reaction of the patient to the anesthetic, and the extent of the rib resection. Usually, the pleural cupola is merely uncapped and the anterior segments of the second, third, and fourth ribs are left as supports for the anterior portion of the lung. At a later second stage these anterior segments are removed to add to the lateral collapse. Because it was noted that there was a definite tendency for the apex to rise an interspace or more during the first 4 weeks after operation, a new step was added. This consists in suturing together the posterior ends of the divided periosteum and intercostal bundles and fastening them down over the depressed apex to the neck of the next intact rib. In this way paradoxical movement of the apex is prevented and the tendency of the apex to rise is combated. The wound is then closed in layers, without drainage.

At the second stage operation, which should never be done in less than 3 weeks, and preferably after 4, no effort is made to inspect the apex. Care is taken not to open into the extrafascial cavity. However, if the apicolysis is to be increased at this stage, one must evacuate the cavity and divide the intercostal bundle and periosteum of the first intact rib. The extent of the rib resection will depend upon the nature and location of the lesion, the reaction of the patient to the first stage, his vital capacity, blood picture, and blood sedimentation rate. An effort is made to

remove enough ribs posteriorly to allow the scapula to fall into the dead space, but this may at times have to be postponed until later.

In some of the cases with large, stiff-walled cavities in the upper lobe, it is necessary to remove all of the anterior segments of the upper 4 or 5 ribs to secure the maximum collapse through the use of external pressure. The proper use of shot bags and pressure pads is essential in some cases. This antero-lateral operation is carried out as a third stage.

In certain cases, when extensive primary resections without apicolysis have failed to produce collapse of a cavity, a revision operation will be necessary. In the cases selected the cavity had been converted from a round one into a narrow longitudinal slit nestling in the paravertebral gutter alongside the bodies of the upper 3 or 4 dorsal vertebrae. Lateral collapse had been sufficient but the cavity was suspended from the apex by ligamentous attachments. In the revision operation, after resection of the regenerated ribs, a line of cleavage was sought in the endothoracic fascia at the level of the third or fourth rib and the lysis carried upward over the apex. In some cases the apicolysis could be accomplished without resecting the first rib. Suture of the divided periosteum and intercostal bundles over the collapsed apex was carried out as in the primary stage of apicolysis. These revision operations are technically next to impossible unless 9 to 12 months have elapsed since the primary operation, as this amount of time is required for thorough calcification of the regenerated ribs. The incompletely regenerated bone is so intimately adherent to the periosteum that it cannot be separated from it. The incision of this periosteum sacrifices the

only chance for a rigid support for the underlying collapsed lung.

Extrascapular apicolysis was performed upon 65 patients during the interval between January, 1936, and July, 1937. An additional series of 8 patients underwent revision operations with extrascapular apicolysis. Except for 1, only patients having apical cavities were subjected to apicolysis.

Certain clinical, laboratory, and x-ray findings were found to be of some prognostic value. These were correlated with the nature of the postoperative convalescence, which was termed easy, moderately severe, or stormy.

Infection of the wounds was present in a rather high percentage of the cases (11.4 per cent). The incidence was much higher in the drained cases (19.6 per cent) than in those not drained (5.9 per cent). Another important factor was the presence of upper respiratory tract infections among the operating room staff during the first part of the period covered by the study.

A vital capacity of less than 35 per cent of the normal was found to be significant of a dangerously low respiratory reserve, and apicolysis in such patients was followed by a moderately stormy or stormy convalescence in 55 per cent of the cases. Only 20 per cent of those with a higher vital capacity had a stormy convalescence.

A smooth convalescence was noted when the white blood cell differential showed less than 70 per cent of polymorphonuclears and more than 20 per cent of lymphocytes.

There were 5 deaths in the series of patients with primary apicolyses, giving a mortality rate of 7.7 per cent.

Cavity closure was accomplished in 88.7 per cent of the completed cases, and a negative sputum was also obtained in 80 per cent.

Of the 8 patients upon whom revision operations with apicolysis were done, 3 died. One death followed accidental opening of the cavity at operation with subsequent severe wound infection. The second patient died of myocardial degeneration and spread of the tuberculosis to the opposite lung. The third patient apparently died as the result of an embolus which became dislodged during the course of an attempt at radical apicolysis in which the pulmonary cavity was accidentally opened. The gravest complications follow the accidental opening of an incompletely collapsed cavity. This opening usually occurred after freeing of the apex and just when an attempt was being made to increase the efficiency of the collapse by separating the medial side of the lung from the third or fourth dorsal vertebra. The residual cavity was invariably found just beneath the visceral pleura, and so intimately attached to the vertebral bodies that separation was impossible without tearing of the lung. Because of this, the separation is concluded at this point. When a cavity is accidentally opened, the thoracoplasty wound should be packed open with vaseline gauze after repair of the tear, and the packing should be changed every day.

Attempt at Resection of First Ganglions of Thoracic Sympathetic in Pulmonary Tuberculosis—H. Gaudier⁹³ performed resections of the second and third thoracic ganglions in patients with pulmonary tuberculosis. The method is a modification of the method described by Alvarez, the ganglions being approached by the dorsal route. Great care should be exercised in the dissection. Dissection of the ganglions and of the nervous ramifications is done by means of a grooved director; then follows anesthetic infiltration and resection of the 2 or 3 ganglions, careful hemostasis, without drainage, and deposition of fragments

of the resected bones. This intervention does not produce the slightest deformity of the thoracic skeleton. This method is accompanied by anatomic modifications which appear to influence favorably the pulmonary parenchyma. Experience may perhaps extend the indications for this treatment to bronchial dilatation or abscess. The resection involves little shock. It should have a place beside the interventions already in practice, the end strived for being the same; pulmonary immobilization and cicatrization.

Production of Venous Stasis and Its Action on Pulmonary Lobes, as New Surgical Treatment of Pulmonary Tuberculosis—R. Valkanyi⁹⁴ believes that Bier's and Kerschner's methods of artificial production of stasis hyperemia in the treatment of pulmonary tuberculosis are not efficient. Extrafocal, selective procedure, is not a pulmonary operation but rather a cardiac intervention, aiming at cure of the lung. In this connection, thoracoplasty, for instance, is likewise not a pulmonary operation but rather an intervention on the thoracic wall. Intervention on the left side is as follows: A transverse, slightly curved incision in the second intercostal space is made which reaches from the left sternal rim to the anterior axillary line. The sternal attachment of the thoracic musculature is pushed aside, and after the second and third costal cartilages come into view they are resected together with from 5 to 7 cm. of the respective ribs. The mammary artery and veins are ligated twice and sections (from 1 to 2 cm.) are resected. The posterior articular ligament of the 2 sternochondral joints is cut into and the sternal attachment of the intercostal musculature is severed and pushed aside. The endo-thoracic fascia and the transverse thoracic muscles are lifted from the pleura and incised. After the pleura has been

mobilized it is pushed aside and a narrow strip of the mediastinal fat tissues and the pleura of the other side come into view. Farther downward, the mediastinal fat tissue becomes wider and passes into the pulsating pericardium. The latter is opened at the lower angle of the incision, at the level of the fourth costal cartilage, behind the sternum. The opening is lengthened to the level of the second costal cartilage. At the level of the upper rim of the third costal cartilage an incision is made which is vertical to the pericardial incision. An anesthetizing fluid is injected into the exposed phrenic nerve. The left lip of the pericardial opening is drawn to the left and the heart is pushed carefully to the right. In the upper angle of the opening, the bulb of the pulmonary artery as well as its left branch become visible, and deeper down and in the caudal direction the left upper pulmonary vein is reached, which is ligated. The procedure on the right side is slightly more difficult. The rather difficult surgical technic necessitates considerable practice on cadavers.

Operation was performed on 5 patients, 1 of whom died. In another patient, the operation produced no improvement in the pulmonary process. In this case the process had existed for a long time and the pulmonary lobe had a number of cicatrized cavities. In such cases the venous ligation is not advisable. In 1 case, with a cavity in the upper lobe, ligation of the vein produced cure in from 4 to 5 months. Two other cases obtained improvement, and in 1 of these complete cure may be expected. The heart was watched carefully after the operation, but in none of the 4 surviving patients was a permanent impairment observed. Electrocardiographic tests made 2 weeks after the operation and repeated several times always disclosed normal heart action. The mode of action of the

lobovenoligature is not completely understood as yet. At any rate its action differs from that of collapse therapy, particularly thoracoplasty. The venous stasis does not cause shrinkage or a compression of the cavernous walls, but a network of strands develops and the cavity becomes filled out.

The Care of the Tuberculous Patient After Leaving the Sanatorium—

J. B. Hawes, Jr.,⁹⁵ agreed that it is important for the patient to be prepared, physically and mentally, for the duties of his job before resuming work and that he should assume those duties gradually. If his former employment is not suitable, a different type of work must be found. A job that entails hard physical exertion, excessively long hours, exposure to dust or bad working conditions, is not suitable. However, it is not practical nor necessary to look for a "light outdoor job."

The patient who is able to resume work must at all times put the interest of his health before his job, if he wishes to continue being well enough to work. He must learn to conserve his energy by not running when he can walk, by not walking when he can stand still, by not standing when he can sit, by not sitting when he can recline.

The placement bureaus or sheltered workshops are of value in obtaining employment for extuberculous patients.

In England, the Papworth industrial colony, which consists of 1500 former patient inhabitants, is working out satisfactorily as a means of rehabilitation for these ex-patients. However, in the United States farm colonies have been unsuccessful. The American working man prefers to work and earn his living and live at home with his family like other working men, so farm and industrial colonies, subsidized by public or private funds, apparently are undesirable in America.

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SYPHILIS

By CARROLL S. WRIGHT, M D.

Syphilis is a disease that can be controlled if proper efforts are applied to that end. Starting with that premise, Dr. Thomas Parran, Surgeon General, U. S. Public Health Service, called a conference in Washington in December, 1936, and started the greatest drive against both syphilis and gonorrhea that this country has ever seen. He made the statement in his address of welcome that leaders in the medical profession claimed that "many physicians are not prepared to give modern diagnosis and treatment." It had been discovered that many State and private laboratories were inaccurate in their examinations, the examinations being so inaccurate in some laboratories that cases of syphilis were being missed, and so hypersensitive in others that certain persons not suffering from syphilis were incorrectly labeled as syphilitic. It was found that many prenatal clinics were still not applying a routine Wassermann test on their admissions. It was found that 11 states had allotted no funds for the control of venereal diseases.

To that conference were invited the leading specialists of the country to map out a plan for venereal disease control and the work has progressed rapidly since

2. 40 per cent of diagnosis depends upon physical examination.

3. Darkfield will identify 65 per cent of genital lesions as syphilitic.

4. Spinal fluid examination is necessary in both early and late syphilis.

5. Examine carefully for visceral manifestations in late syphilis.

6. Make routine serological examination in pregnancy.

Control of syphilis depends chiefly upon the diagnosis and efficient treatment of early syphilis. It is essential that cities and States make good laboratory facilities easily available to every physician and that provision is made for supplying free drugs for the treatment of the poor. To make laboratory facilities and drugs available is part of the plan for the control of syphilis and as physicians we must not fail to make use of these provisions.

Diagnosis of syphilis must be prompt and accurate. The serologic blood test, becoming positive within 2 or 3 weeks after the onset of primary syphilis and remaining positive in the vast majority of untreated patients throughout the entire course of the disease, is the most important evidence of the existence of syphilis. That it is, therefore, imperative that only those serologic tests of proved efficiency be made available to private physicians and health officers is emphasized in Venereal Disease Information.¹

New Serologic Tests for Syphilis

—Commercial concerns are offering for sale to general practitioners relatively new and unestablished serologic test outfits containing antigen and other materials. The claim is made of rapid diagnostic work sufficiently accurate to guide any physician in his treatment of patients with syphilis. The fact that the antigens are crude and may deteriorate is not men-

DIAGNOSIS OF SYPHILIS

As pointed out by Godfrey, New York State Commissioner of Health, "Efforts to control syphilis are perhaps more closely related to diagnosis and treatment than is true of any other communicable disease." Certain rules for the diagnosis of syphilis are worthy of emphasis.

1. 60 per cent of diagnosis depends upon the laboratory.

tioned, nor that the dye materials incorporated in the antigens are useless to a trained serologist. In current comment, the Journal of the American Medical Association² discusses the dangers attending the use of these test outfits.

Warning is not given of the danger which is always present in serologic procedures carried out with whole blood or of the complete reversal which inactivation may induce. A most grievous omission is the failure to recommend the use of positive and negative control serums as guides in the interpretation of the test. It is not admitted that these methods have had only a limited practical test in hands other than those of the originators.

Thus, active commercial promoters may place in the hands of the individual physician everywhere a diagnostic function which is acceptable as efficient only when performed in laboratories adequately equipped and staffed by trained personnel. The science of serology has not as yet progressed to a degree of simplicity at which the detection of syphilis may be placed on a basis comparable to the detection of albumin in the urine. It is difficult to see how any premature steps in this direction can do other than work to the detriment of the patient with syphilis.

Multiple Tests in the Serodiagnosis of Syphilis—A plan of using a multiple test method for routine study is described by L. F. Pierce, H. A. Patterson, R. A. Stevenson, and H. C. Torbert.³ In this routine all bloods are tested by the methods of Eagle and Kline. If 1 or both give a positive or doubtful result, the Kolmer quantitative Wassermann is performed. In the event of disagreement, at least a second specimen is subjected to all 3 tests unless the patient is known to be under treatment.

The author's results also show that the multiple test method materially lessens

the danger of reporting false positive results. The Kolmer-Wassermann seems well adapted to this method. Its sensitivity is less than either of the precipitation-flocculation tests used, but this fact only adds to its value as a flag against false positive results. It is emphasized that the complement fixation test is not carried out with the thought that its alleged "quantitative" features will throw significant light on the actual progress of the disease in the patient.

In the small proportion of discordant cases that will arise with even the most careful technic, and with any routine series of tests, other tests should be freely called upon and interlaboratory checks instituted. To insure comparability of cross checks, however, it is essential to know the methods used in the checking laboratory in the most specific detail, the source of reagents, and what, if any, efforts are made in the way of voluntary periodic cross checking with others. At least 1 test should be the same to the finest detail in each laboratory for the comparison to have real value.

Finally, it cannot be said too strongly that there are patients suffering from syphilis whose bloods and spinal fluids react negatively to all tests. Conversely, it is known that there are patients who do not have syphilis—for example, lepers, malarial patients, some febrile patients—who react positively to from 1 to all tests, though perhaps not to all at the same time. Therefore, it cannot be said that, in any real sense, a positive or doubtful report stigmatizes any patient. This concept of serology makes possible the acceptance of a much desired ideal, *i. e.*, the doing of routine blood tests. The best the serologist as such can do is to impose upon the clinician the duty of reconciling the results of a series of reports with the clinical condition of the

patient. The available serodiagnostic tests are procedures of high accuracy, but the diagnosis of syphilis can never and should never be made by the serologist. This is the responsibility of the clinician, and it cannot be dodged. To put it in another way, the viewpoint of the serologist must essentially be that of the actuary. He may speak with great confidence of the number of syphilitics represented by a thousand blood tests on as many individuals. With respect to the significance of a test on 1 person, he can say nothing beyond citing the law of probability.

In a similar study, T. M. Vogelsang⁴ reports the results of the simultaneous performance of 4 different serologic tests for syphilis upon 6000 sera. Identical results with all 4 tests (Kahn, Meinicke II, Muller II flocculation, and the water bath fixation complement fixation reaction) were obtained in 86 per cent of patients known to have syphilis. The author feels that by parallel performance of various tests one obtains a greater diagnostic certainty than by the performance of 1 single method.

A Micromodification of the Eagle Flocculation Technic—A micromodification of the Eagle flocculation technic which can be performed with blood obtained from a finger tip is described by H. Eagle and A. F. Brand.⁵ They believe that the new procedure is more sensitive than the original macroprocedure, that it is specific, and that it is more easily read by the average technician.

The antigen prepared from beef heart and fortified with cholesterol and corn germ sterol is the same as that previously described for the macrotest. Two volumes of 0.85 per cent NaCl are rapidly blown into 1 volume of antigen to form stock dilution, which keeps for 5 days, if stored in the ice box. Immediately before use, 1 volume of this stock dilution

is further diluted with 8 volumes of 4 per cent NaCl.

The serum is inactivated at 55° C. to 56° C. for 20 to 30 minutes. To 0.1 cc is added 0.05 cc of the final antigen dilution—if more serum is used, the antigen is increased in proportion. The mixture is shaken for 2 minutes, the tubes placed in a 37° C. water bath for 30 minutes, then centrifuged for 10 minutes at 1500 to 2000 rpm, and read at once. In case of emergency, as for transfusion the inactivation can be shortened to 3 minutes at 60° C. The tubes are shaken for 5 minutes and the usual incubation is omitted. The tests are then centrifuged for 8 minutes and the results are read at once. The entire test can be completed in 20 to 25 minutes with only a slight decrease in sensitivity.

Data are given showing the relative sensitivity of the new micromodification, the old macroflocculation technic and an ice box Wassermann test. The new microprocedure detected 86.1 per cent of a group of 503 serums from syphilitic patients under treatment or observation. The old macroprocedure detected 78.7 per cent and the ice box Wassermann technic with a highly fortified antigen detected 67.1.

In 469 selected patients from the private wards, 455 gave a negative microtest and 14 gave a positive microtest. Of the latter 10 were seropositive by a rigidly specific Wassermann technic; 1 gave a definite history of syphilis and treatment, in 1 the clinical findings were strongly suggestive of syphilitic infection, and the remaining 2 were not available for clinical or serologic study. In this series of 469 patients with a variety of clinical conditions, there were no demonstrable false or doubtful reactions. In confirming this conclusion in a control group of 125 probably nonsyphilitic individuals (medical students, nurses, physi-

cians, and technicians) there was 1 doubtful result, confirmed by a repeat test, in a person who was available for clinical study.

The Provocative Phenomenon in Syphilis—In *Queries and Minor Notes*,⁶ a physician asks the questions, "What dose of arsphenamine should be used for a provocative test for syphilis?" and "What is the time between the giving of the drug and the taking of blood for the Wassermann test?" These are such pertinent questions that the answers are worthy of repetition.

Studies of the provocative phenomenon in syphilis so far carried out are inconclusive on 3 scores: (a) The dosage of the arsenical to be employed, (b) the proper time interval between tests after treatment and (c) the use up to this time of a qualitative rather than a quantitative serologic technic. Such information as is available indicates that in all patients with early syphilis and in the majority of those with late syphilis, the first injection of a therapeutic dose of an arsphenamine (*e g.* arsphenamine 0.3 to 0.4 Gm, neoarsphenamine 0.45 to 0.9 Gm, mapharsen 40 to 60 mg, and so on) is followed within 5 to 7 days by a quantitative rise in reagin titer, which falls to or below its original level by the fourteenth day after treatment.

The provocative test is of no value whatever as a determinant of "cure" in a patient who is seronegative following treatment, since the provocative phenomenon often fails to appear in individuals whose subsequent course includes definite progression or relapse.

Almost the only circumstance in which the provocative test is of value is for the confirmation of the diagnosis in individuals previously untreated, in whom the presence of syphilitic infection is suggested by a low titer reagin content of the blood, *i e.*, those in whom doubtful

or weakly positive serologic tests are obtained. In such persons the administration of a therapeutic dose of an arsphenamine is often followed by a quantitatively measurable increase in reagin titer, and if such an increase occurs the diagnosis of syphilis may be regarded as confirmed.

The suggested procedure is: (a) A preliminary serologic test on a quantitative basis, (b) the intravenous administration of a therapeutic dose of any of the arsphenamines, (c) repetition of the quantitatively titered serologic test at 48-hour intervals for a minimum of from 10 to 14 days.

No reliance should be placed on the result of the tests unless the laboratory is prepared to furnish quantitative titrations.

Treatment of Syphilis

Present Day Weapons Against Syphilis—We are fortunate in having available a formidable therapeutic armamentarium with which to fight syphilis. Prior to 1910 the physician was limited to mercury and iodides and syphilis was regarded as incurable. Let us contrast this with our present day therapy.

1 ARSENICALS

Arsphenamine (606).
Neoarsphenamine (914).
Sulfarsphenamine
Silver arsphenamine.
Neosilverarsphenamine
Mapharsen
Acetarson (stovarsol)
Tryparsamide

2 BISMARSEN (combining As and Bi)

3 BISMUTH.

4 MERCURY

5 IODIDES.

6 FEVER THERAPY

Of this list, sulfarsphenamine is little used today because of the local pain it produces and its tendency to cause skin eruptions; silver arsphenamine and neo-silverarsphenamine are unpopular chiefly

because of the difficulty of administration and the danger of argyria. The following table briefly outlines the virtues and faults of the more commonly used anti-syphilitic drugs.

CHOICE OF DRUGS FOR SYPHILIS

- 1 ARSPHENAMINE (606):
Therapeutically the most effective.
Higher toxicity.
Difficult to administer.
- 2 NEOARSPHENAMINE:
Therapeutically inferior to arsphenamine.
Less toxic than arsphenamine.
Easily administered.
- 3 MAPHARSEN
A trivalent arsenical, first studied by Ehrlich
Given in small doses (0.03 to 0.06 Gm.)
May be used in place of neoarsphenamine
- 4 TRYPARSAMIDE
Used only in central nervous system syphilis.
- 5 ACEIARSON
Chiefly given by mouth
Chief value is for congenital syphilis
- 6 BISMUTH
Seven-tenths the therapeutic value of neoarsphenamine
Given conjointly or alternately with neoarsphenamine
Rarely causes toxic symptoms
- 7 MERCURY
Four-tenths the therapeutic value of neoarsphenamine
Always incorporate in a treatment plan
Give in short courses
Injections or intramuscular injections best

There has been considerable discussion as to the value of the iodides. They certainly have no spirocheticidal action and are of no value in controlling infectiousness. Fever therapy is chiefly of value in the treatment of central nervous system syphilis.

Because of the difficulty of administration, arsphenamine, although therapeutically superior to neoarsphenamine, is lit-

tle used by the general medical profession. The convenience of administration of neoarsphenamine and its lower toxicity are advantages that cannot be easily disposed of, and when rightly used the chances of success are almost equal to arsphenamine.

PRINCIPLES OF TREATMENT FOR EARLY SYPHILIS (MOORE)

1. Treatment must be continuous
2. Treatment must continue from 15 to 18 months regardless of the Wassermann reaction
3. To control infectious relapse give a minimum of 20 injections each of an arsenical and a heavy metal
4. To accomplish individual cure, a minimum of 30 injections of an arsenical and 60 of a heavy metal are desirable
5. Life-long posttreatment observation with periodic re-examination is essential to determine the fact of cure

The following is a suggested plan of treatment for early syphilis.

TREATMENT PLAN FOR EARLY SYPHILIS

1ST TO 17TH WEEKS—Neoarsphenamine, 0.3 to 0.6 Gm.*

EACH WEEK—Bismuth, 100 to 200 mg

17TH TO 21ST WEEKS—Mercury injections, 4 to 6 Gm daily, or mercury salicylate injections, 1 to 2 Gm weekly

21ST TO 35TH WEEKS—Neoarsphenamine, 0.3 to 0.6 Gm

EACH WEEK—Bismuth, 100 to 200 mg

35TH TO 39TH WEEKS—Mercury

39TH TO 65TH WEEKS—If Wassermann is negative give alternate courses of bismuth and mercury, with a preponderance of bismuth

65TH TO 120TH WEEKS—Probation Blood Wassermann every 3 to 6 months

Follow with complete physical and neurologic examination

Keep under observation throughout life

Any treatment plan may require revision depending on the tolerance of the patients to the drugs used. For instance, mapharsen may be used instead of neoarsphenamine. Occasionally a patient

* Mapharsen, 0.03 to 0.06 Gm. may be substituted.

will tolerate none of the arsenicals and then bismuth and mercury must be pushed to the limits of tolerance, with an excellent chance of a good therapeutic result.

INTERESTING FACTS CONCERNING SYPHILIS THERAPY

1 Every day of treatment continuity in the first 6 months of infection means less relapse, less resistant serology, less visceral, vascular and neurosyphilis for the future

2. Treatment discontinued between the first and fourth injections of arsenic means 65 per cent relapse. If from 5 to 9 injections are given there is only 14 per cent relapse.

3 Continuous treatment begun in seronegative primary syphilis yields 86.4 per cent satisfactory results; 64.3 per cent in the seropositive primary stage and 81.5 per cent satisfactory results if begun in the secondary stage.

With this preliminary review of a few of the points emphasized in the battle being waged against syphilis, let us turn to the literature of the past year for new and important contributions to this subject

Methods and Policy in the Control of Syphilis—The present status of venereal disease control work as a public health problem in the United States has been presented in outline form by J. H. Stokes and V. C. Garner.⁷ Annually 500,000 cases of early syphilis seek authorized medical care. A large percentage of individuals acquire syphilis before the age of 20 years. In spite of the upward trend of heart disease, there has been some decrease in cardiovascular syphilis. In general, the figures cited show that syphilis is a major health problem in the United States today and that the disease is not on the decline, although public health measures are showing some successful results

Articles regarding the medical situation with respect to syphilis show that about 55 per cent of all the physicians engaged in private practice in the United

States do not treat syphilis, and slightly more than 50 per cent of all syphilitic patients are treated in clinics.

Studies regarding the amount and kind of treatment given show that the continuous system is used most frequently in the United States.

The international investigation by the League of Nations' Commission of Experts disclosed shocking inadequacies in diagnosis and treatment among the selected clinics of the world.

The possibility of the prevention of transmission of syphilis has been demonstrated in the treatment of syphilitic pregnant women and the control of congenital syphilis.

Suggestions have been made that a serologic examination for syphilis should be made a routine procedure in the examination of some 7,700,000 annual admissions to medical and surgical beds in hospitals and in the examination of all outpatient and dispensary cases. If this should be done, it is estimated that some 3,000,000 new syphilitic patients would be found annually. Such a procedure would require large appropriations and trained leadership.

The impossibility of providing adequately trained personnel for handling syphilitic problems is evident from the fact that in 58 of 63 undergraduate medical schools in the United States inadequate instruction is provided in syphilology.

Those in charge of the American control program are proceeding cautiously, taking into consideration the advantages and difficulties of the work. The work of the Co-operative Clinical Group is of primary importance in its investigations of the values of various types of treatment, especially that of modern fever therapy. The assistance of the press, national broadcasting companies, various social and educational organizations in

promoting public interest in this problem has been invaluable.

According to O C Wenger,⁸ the successful administration of control program for venereal diseases requires adequate funds, experienced personnel, and reliable data concerning the extent of the problem.

Assuming that funds and trained personnel are available, reliable information should be secured showing: State appropriations, regulations and facilities for the control of venereal diseases, methods of notification of venereal diseases used in the community, free clinic facilities available, laboratory service available, distribution of drugs, hospital facilities, regulations governing prostitution and quarantine measures; industrial control measures, educational program for schools and civic organizations; regulations governing the sale of prophylactic measures; and the general attitude of the medical profession toward a proposed venereal disease control program.

It is recommended by P Warner and Benjamin Warner⁹ that all private physicians conduct routine serologic examinations of their patients and be on the alert to find new cases of syphilitic infection.

Jaundice from Bismuth—Jaundice occurring during the treatment of syphilis has been the subject of a great deal of study. When medication has been thought to be the cause of the jaundice, the arsphenamines have been blamed in almost every instance. Graftar,¹⁰ in a series of 246 cases of jaundice, observed it in 7 persons who had received bismuth compounds alone and 14 more to whom arsphenamine had last been given a year or more previously. In a recent report by R. Nomland, E. A. Skolnik and L. L. McLellan,¹¹ 75 cases in which jaundice occurred during therapy for syphilis were studied. In 32 the cause was thought to

be a bismuth compound. In these 32 the jaundice began within 6 weeks after the last treatment. Ten of the patients had had only the bismuth compound. Twenty-two had had neoarsphenamine, but none within 12 weeks of the onset of the jaundice; in 15 cases more than 15 weeks had elapsed since the last treatment with neoarsphenamine. All of the patients with bismuth jaundice recovered, and most of them were subsequently given a bismuth compound without its causing harm.

The Patient's Problem—There is only silence on 1 point of the recent clamor and publicity concerning syphilis: What is the patient's attitude toward his disease and toward society? L. B. Ingraham¹² believes that if we understood this 1 vital subject, we might come a little nearer to providing a note of real hope. It is the patient who will tell why we don't stamp out syphilis. He it is who goes no more for treatment. He it is who gives a false name, who moves to the unknown address, who thoughtlessly infects others. It is the patient, then, who holds our success in the hollow of his hand! Ingraham considers the point of view of the patient from (a) the stigma of diagnosis, (b) readjustment of his whole manner of living, and (c) the problem of treatment.

We are all familiar with the known history of the invasion of Europe by syphilis. Public health measures of that day were full of shame for the unfortunate patient. In 1496, infected persons had to leave Paris within 24 hours. Out of Scotland it was ordered "for the protection from disease, all light women must desist from their vice and the sin of venery. They must work for support, on pain else of being branded on the cheek with a hot iron." Infected persons were banished from Edinburgh to an island near Leith. In the nineteenth cen-

tury in an Eastern city of the United States "persons suffering from venereal diseases were excluded from a dispensary as victims of their own sensual indulgence" At the time of the World War, syphilis, gonorrhea, and immorality became synonymous In California there was a campaign to legislate venereal disease out and clean living in. The draft revealed the enormous number of persons in the United States suffering from syphilis and gonorrhea. Pamphlets were distributed, movies shown, and lectures given which in many cases brought horror and fear rather than intelligent understanding of the disease.

Not only does the patient have to face and accept a bitter potion when he hears his diagnosis pronounced, but he must often readjust his whole manner of living This is the second great problem with which the patient is confronted Suppose the infectious individual works as food handler, beauty operator, barber, or domestic; he frequently learns that employment must be suspended There are explanations to be made not only to the employer, but also at home The patient doesn't want to lose his job or the respect of his associates He fears that when others know the diagnosis they will shun him The husband or wife with infectious syphilis has a home situation to face Marital relations must be suspended and there are explanations to be made The problem of previous sexual infidelity must be faced There must be no more pregnancies for the syphilitic mother The single person must postpone the marriage he had planned Precautions against infection of others need to be observed in a hostile household without arousing suspicion The patient must take responsibility for arranging the examination of contacts and exposures to the infection, an often humiliating business.

And now we come to the third phase in the problem of syphilis control as it confronts the patient, that of treatment. From the standpoint of medical science, the problem has been largely solved, but it is far from simple as viewed by the patient. To be sentenced to a year or more of continuous treatment is no small matter, especially if one's symptoms disappear in 2 or 3 weeks and one feels perfectly well thereafter. Treatment is expensive; the clinic may be inconveniently located. The family often is poor and cannot pay the fees; there is no money for carfare. Hours of employment may be such that "time off" for clinic attendance cannot be arranged. There is a long, tiresome wait Indeed, in many instances we must deal with the plight of the patient where treatment is not available in his community and he cannot afford private care.

A distinguished public health officer has said "the control of syphilis must depend upon the extent to which the patient can be trusted; how well he can be trusted depends upon how carefully he has been instructed" The first case-holding principle, therefore, is the education of the patient in the clinic, in the office, and in the home Instruction should begin with a reasonable explanation of syphilis as diagnosed in each particular case by the physician The first interview can determine to a large extent the entire future course of the successful relationship between the patient and the clinic The interview establishes the confidence of the patient. It presents to him the diagnosis of syphilis as a disease and not as a moral problem implying the fear of reproach or disgrace It gives him a practical knowledge of infectious precautions, void of absurdity or of extremes in over- and undercaution It is an attempt to forestall his lapse from treatment It prepares the way and often completes the

necessary arrangements for examination of contacts. But the teaching of the patient does not come to an end with this preliminary interview. It reaches him at every point when misunderstanding might discourage or doubt weaken his ability to complete his course of treatment. All patients with syphilis must be taught something, and the instruction is always guided by the mode of infection, stage of the disease, the status of the patient, and the requirements of treatment.

Criteria Governing the Use of Antisyphilitic Drugs—In considering a drug worthy of use in the treatment of syphilis, H. N. Cole¹³ lists the following criteria:

1. The drug should be cheap enough to be available to all, perhaps it should even be furnished by the State, as in Denmark.

2. It should be in as simple a form as is possible, not requiring a too elaborate technic for its administration. Because of this criticism our most potent antisyphilitic remedy, arsphenamine, is rarely employed outside syphilis clinics and hospitals. Neocarsofenamine and mapharsen are more easily administered.

3. The remedy should be free from attendant unpleasant symptoms—pain, nausea, emesis, headache, etc. Moreover, severe systemic after-effects should not follow its use.

4. It is felt by some, notably Stokes, that the ideal preparation should not even require as complicated a method of administration as the intravenous route; in other words, intramuscular therapy would be simpler.

5. Its action should be relatively rapid in alleviating acute symptoms of syphilis; thus a remedy requiring more than a day or so to destroy the treponemes in moist papules on the lips is not sufficiently potent.

6. The *summum bonum* in the antisyphilitic drug is the preparation that at 1 dose will destroy all the organisms of the disease in the body without attendant harm to the host. This was Ehrlich's idea when he announced his 606th trial compound. Unfortunately, it failed to satisfy the requirement. So we are now forced to rely on the drugs that will come closest to this desideratum without too severe reaction on the host. Experience has shown

that the 3 heavy metals in their proper salt, arsenic, bismuth, and mercury, best answer these requirements.

After a rather full discussion of the various types of drugs used in the treatment of syphilis, Cole asks the question, "What forms of therapy should be used in the treatment of syphilis?" He states that it is not the object of his paper to outline a course of medicaments to be used for every case of syphilis, but rather to mention some principles suited to the type of patient encountered. One should always keep in mind that, provided there are no contraindications, there is no drug like the arsenical to "blanch out," as the French call it, the acute contagious lesions of early syphilis. Either the *arsphenamines* or *mapharsen* may be employed for the purpose. On the other hand, if we are dealing with *cardiovascular syphilis* or a *severe hepatic involvement*, the arsenicals are *contraindicated*, at least for the time being, and if they are ever employed it should be very cautiously. Here one of the other heavy metals, either *bismuth* or *mercury*, may be given.

Probably best results will be achieved through the use of a preparation that is able to furnish a therapeutic level of the metal in the blood stream in a comparatively short period of time, *e g*, daily *mercury succinimide* or *biniiodide* injections, biweekly injections of *iodo-bismitol* or triweekly injections of *sodium bismuth tartrate* or *thioglycollate*. Recent studies have revealed that *thio-bismol* gives a very rapid and quite high urinary excretion which falls even as rapidly within 24 hours after the injections. The preparation is apparently absorbed very rapidly and as rapidly excreted. In fact, this is so much the case that even with successive injections, unless they are given at least 3 times a week, the amount of bismuth in the blood

stream cannot be kept at a therapeutic level. There is practically no cumulation as revealed by the urinary curve of excretion. With iodobismitol, on the other hand, there is a slightly slower absorption so that even with injections given possibly only twice a week the bismuth level in the circulating blood tends to cumulate and rise to an appreciable therapeutic zone.

Sodium bismuth tartrate, aqueous solution, seemed to be midway between the thiobismol and iodobismitol in this respect. Again the iodobismitol in its urinary excretion curve seemed to be midway between the water soluble bismuth preparations and the so-called liposoluble preparations, *bismocymol*, *quinio-bine* and especially *biliposol*. These preparations are quite efficient in attaining a therapeutic level in the blood stream and holding it for a reasonable length of time, particularly the last named. Its price, however, precludes its general use. A previous study has shown that a satisfactory early rise of bismuth level in the blood stream with sustained cumulative effect can be attained by a suspension in oil of *sodium potassium bismuth tartrate*, 48 or 64 mg. per cc., a peak level of 3.4 mg excretion in the urine being attained after the third injection of only 1 cc. If it is desired to get a slowly rising cumulative bismuth excretion curve in the urine, this may be achieved by the use of weekly injections of the *bismuth salicylate* over a period of 10 to 12 weeks. It is slowly absorbed and the effect is consequently slow in starting. Hence, if it is being given in conjunction with arsenicals as in-between therapy, its exhibition should be begun with probably the last 1 or 2 injections of the arsenical.

How much bismuth should a patient receive in order to get a satisfactory therapeutic action? Lomholt, working

with an aqueous suspension of the bismuth oxychloride, estimated that the patient to have a satisfactory dosage, should receive 0.5 mg. metallic bismuth per kg. per day. This preparation in the water suspensions is one-half absorbed in 10 days and one-third is excreted. Naturally, if one were working with an oil suspension where there is a slower absorption and excretion, it might be dangerous to apply this rule. It probably would be safer to employ a preparation that will give, under its method of administration, a more or less continuous urinary excretion of 2, or better 3 or 4 mg., of the metal daily. This would indicate a satisfactory, continuous therapeutic level of bismuth in the blood stream. Such a type of curve can be achieved with injections 3 times a week of sodium bismuth tartrate or of thio-bismol or with biweekly injections of iodobismitol; with liposoluble preparations it certainly would be possible with weekly injections of bismo-cymol or biliposol and with injections of an oil suspension of sodium potassium bismuth tartrate, 64 mg. metallic bismuth per cc. Again it may be achieved, though more slowly, with the bismuth subsalicylate 0.125 Gm. metallic bismuth weekly.

Naturally, if one were working with a water soluble aqueous preparation, the excretion would drop very rapidly on discontinuance of the injections. With the iodobismitol, however, our studies showed a respectable afterperiod of satisfactory urinary excretion. The longest sustained afterperiod would be seen with the bismuth subsalicylate, though it is doubtful whether a prolonged excretion of perhaps 0.5 mg. per day would have any therapeutic significance. It would probably represent not bismuth absorbed from an injection site, but rather slow absorption into the blood stream from various depots throughout the body.

Moreover, with all the bismuth and mercury salts as well, it must be remembered that the excreted metal should be in a form that is shown to be therapeutically active. Years ago Lomholt suggested that a large part of the radical in excreted mercury salicylate was in a fixed form of no therapeutic value. Thus with a new preparation it is necessary to link up experiments in acute human syphilis with other data before definite conclusions can be drawn.

In view of the findings of Cannon and his coworkers, and in the light of previous experiments, the syphilographer should remember that there is a drug, mercury. Moreover, occasions may arise, particularly with arsenic-sensitive persons, when it may be necessary to alternate courses of mercury with bismuth. Thus one might employ a series of 60 to 80 *inunctions of unguentum hydrargyri fortius* in place of courses of bismuth. Some years ago it was shown that by careful munction of 30 mg. of 30 per cent mild mercurial ointment once a week given by a masseur, a very satisfactory mercurial effect could be achieved; or, again, a series of 10 to 12 injections of mercury salicylate might be administered, giving them once in 5 to 7 days.

In concluding Cole states that:

1 The ideal antisiphilitic drug will be of a high chemotherapeutic ratio, *i e*, having a low toxicity for the human body and yet a high potency for *Spirochaeta pallida*.

2 The preparation should be easily administered and inexpensive.

3 The arsphenamines and mapharsen are the ideal agents for eradicating acute infectious lesions of syphilis.

4 In using bismuth preparations it is necessary to administer the salt frequently enough to keep continuously a therapeutic level of the metal in the blood stream. This may be conveniently measured in terms of excretion of bismuth in the urine—around 2 to 4 mg. of bismuth daily.

5 Such a level can be achieved with aqueous or ethylene glycol solutions of the following preparations:

Triweekly injections of thio-bismol, 2 cc.
225 mg. metallic bismuth.

Triweekly injections of sodium bismuth tartrate, 2 cc. 64 mg. metallic bismuth.

Triweekly injections of iodobismitol, 2 cc.
50 mg. metallic bismuth.

The same can also be achieved by weekly injections of the following oil soluble compounds:

Bismo-cymol, 2 cc. 100 mg. metallic bismuth.

Biliposol, 2 cc. 80 mg. metallic bismuth.

Or of the following oil suspensions (weekly):

Sodium potassium bismuth tartrate, 1 cc.
48 mg. metallic bismuth.

Sodium potassium bismuth tartrate, 1 cc.
64 mg. metallic bismuth.

Bismuth salicylate, 1 cc. 125 mg. metallic bismuth.

6 When a rapid bismuth action is desired the bismuth preparations dissolved in water or in ethylene glycol are indicated. For a slower and more sustained action the oil soluble or oil suspension preparations should be employed.

7 The use of mercury in the treatment of syphilis should not be forgotten, particularly in the later stages of treatment.

Sodium Thiosulfate in the Treatment of Arsenical Dermatitis. The administration of sodium thiosulfate for the treatment of arsenical dermatitis has been an accepted procedure among dermatologists ever since it was first introduced by Ravaut in 1920. In this country McBride and Dennie confirmed the value of the treatment, and since then numerous clinicians have attested its value in shortening the duration and lessening the severity of arsenical eruptions, especially postarsphenamine dermatitis. S. Ayres, Jr., and N. P. Anderson¹⁴ point out that a number of investigators have shown that the administration of *sodium thiosulfate* orally or intravenously causes a prompt and pronounced increase in the elimination of arsenic, followed in the course of

several weeks by a gradual diminution in the output of urinary arsenic, to the point where only traces or none at all can be detected, although it must be admitted that carefully compiled statistical studies have not been numerous. Some conflicting reports, however, have appeared, notably those of Young and of Mattice and Weisman. Moore, in his textbook on the treatment of syphilis, made the rather dogmatic statement that he had seen no evidence that the drug is of any value whatever. M. B. Sulzberger and J. Goodman¹⁵ apparently accepted the conclusions of Mattice and Weisman as the last word on the subject when they stated:

It seems that still another fallacy regarding arsenic excretion has been uncovered by Mattice and Weisman, who . . . demonstrated that . . . far from increasing arsenic excretion, the administration of sodium thiosulfate actually decreased the urinary output of the metal. Inasmuch as no satisfactory clinical proof of the efficacy of sodium thiosulfate in the therapy of arsenical dermatoses has been adduced, it would seem that, in the light of these new experimental findings, the drug may actually do harm rather than good.

Ayres and Anderson believe that such diametrically opposed points of view call for a reappraisal of the entire subject. A matter of this sort is susceptible of quantitative investigation. It would appear unfortunate, therefore, that Sulzberger and Goodman should accept the conclusions of Mattice and Weisman as definitive in the face of a considerable volume of clinical and experimental evidence to the contrary, especially since Mattice and Weisman drew their conclusions from observation of only 4 patients, of whom none was suffering from arsenical dermatitis and 1 was not even suspected of having an arsenical disorder.

The authors state that they have for a number of years been interested in the

subject of arsenic as an etiologic factor in certain disorders of the skin and have made a practice of regularly testing the urine for arsenic before and immediately after the injection of sodium thiosulfate in all cases of suspected arsenical causation with the exception of cases of frank postarsphenamine dermatitis, of which they have fortunately seen but few during recent years.

A statistical study of 49 cases of various dermatologic conditions in which arsenic was suspected of being a causative factor and in which arsenic determinations were made on the urine before and immediately after a single injection of sodium thiosulfate demonstrates clearly that an increase in the excretion of urinary arsenic usually follows the injection of sodium thiosulfate.

Transfusion Syphilis

Sixty-eight proved cases of syphilis transmitted by blood transfusions have been recorded in the literature according to C. R. Rein, F. Wise and A. R. Cukerbaum¹⁶ but the total number of such cases must be much greater, as the majority of such accidents remain unreported. Serologic tests of blood donors at intervals from 1 to 6 months do not guarantee against infection with syphilis through blood transfusion. Donors with a negative reaction on a previous examination have ample opportunity to acquire syphilis during the time interval which is permitted.

Control can be accomplished only by testing the donor's blood immediately prior to every transfusion. The flocculation tests are especially applicable for this purpose, because they possess a high degree of sensitivity and specificity, and, in addition, some of them can be performed in a few minutes with a small amount of blood easily obtainable from a puncture in the finger. The sensi-

tivity of the test is of great importance, as insensitive tests may give negative results in the early stage of the infection (immediately after the appearance of the chancre). The Kline flocculation tests (diagnostic and exclusive tests) are the most suitable ones, because they can be performed more expeditiously than any other flocculation test of high specificity and sensitivity, and they are more dependable in the detection of syphilis in its earliest stage.

The authors describe in detail a rapid method of typing, crossmatching and testing for syphilis of blood of donors. The whole procedure takes about 30 minutes, during which time the donor can be examined for clinical signs of syphilis.

Taking part in the discussion that followed the reading of this paper, Raziss declared that judging by experiments on rabbits, a negative serologic test affords no absolute assurance of freedom of the blood of the donor from spirochetes. He found that rabbits inoculated with syphilis intratesticularly contain spirochetes in the blood as early as 5 minutes after the inoculation and continue to harbor them for weeks afterwards. The presence of spirochetes has been established by the biological method, *i. e.*, by inoculating normal rabbits with the blood of the animals to be tested. By the same method, the presence of spirochetes was sometimes revealed in the blood of animals which have been inoculated with syphilis 2 or 3 years earlier, *i. e.*, animals with latent syphilis. By analogy, it may be concluded that latent syphilitics may sometimes carry spirochetes in their blood.

Stokes remarked that there are seronegative syphilitics who can transmit syphilis, and a thorough study of the donor, particularly the professional donor, is therefore a necessity. He also

observed that tests for syphilis should be made in all cases where biologic fluid (*e g*, convalescent serum) passed from 1 patient to another.

Syphilis Epidemiology

According to N. R. Ingraham, Jr.,¹⁷ the ultimate success of the extensive campaigns which have been inaugurated in the attempt to prevent the spread of syphilis by adequately treating the infectious syphilis carrier depends upon application of practical epidemiological methods. In controlling the dissemination of this genitoinfectious disease by the prompt institution of medical treatment it is necessary to discover the majority of the foci from which the disease is spread; yet it is well known that these foci are often migratory, that their infectious stage may be transitory and not recognized by the patient, that their identification is still too frequently hidden and protected by custom and social prejudices. If the transmission of the disease is to be arrested in this manner, the patient with a recently required infection must come *early* under adequate medical supervision, he must *usually* know approximately where he has acquired his disease, and he must *ordinarily* be willing to divulge the exact identity of all individuals with whom he has had intimate contact during the assumed period of his infectiousness. The various alleged contacts once identified must first be located, then persuaded or compelled to submit to medical examination, and finally, if found infected, must be induced to submit to an exacting treatment extending over a period of a year or more. This shows that the most important link in the chain is the infected patient.

From a comprehensive study of the problem of venereal disease contact-tracing and case holding in an urban and semiurban population made by the

Bureau of Venereal Disease Control of the New Jersey State Department of Health, Ingraham suggests that the employment of a confidential persuasive approach to elicit a voluntary response from the patient, in the hands of a trained individual, is about half again as productive of usable epidemiologic information as is the untrained coercive approach. The voluntary response method is likewise superior to compulsive methods in persuading the average suspected contact to submit to medical examination and to about the same degree. In clinic practice women are apparently more apt to give usable epidemiologic information than are men, and the colored are more co-operative than the white though the personality of the interviewer doubtless affects these responses considerably.

Ingraham reports that in the average clinic, where little effort is made to induce the patient to continue under observation, from 70 per cent to 90 per cent of the patients disappear within a year before the minimum standard of treatment can be given. In other words, less than one-third can be held. Adequately instructing the average new patient as to the public health implications of his disease, emphasizing the necessity from a personal standpoint of his continuing treatment, is capable of improving clinic attendance only about 5 per cent. An active follow-up service with a threat of compulsion when necessary, and the occasional application of the "teeth" of the law to bite the recalcitrant offender is capable of holding 70 per cent of the early infectious cases for the required period of time. Colored patients conform to treatment standards much less readily than white. The white man is the most susceptible to obligatory treatment methods, the colored man and woman next, and the white woman least

of all. The combined cost of contact tracing and case holding per new patient per year in the 2 clinics surveyed amounted to \$11.36 and \$16.58, respectively.

The Control of Syphilis in Industry

Health programs in industry have demonstrated their value, but A. E. Russell¹⁸ believes insufficient emphasis has been given to venereal disease work. Dr. Parran in his recent book and in other writings has called attention to the fact that industry is paying heavily for syphilis. The disease is usually fatal in middle life, the period in which a man's life is of most value as related to industry. The efficiency of a syphilitic worker is affected in direct proportion to the stage of the disease.

Russell condemns the policy of discharging an employee infected with syphilis and recommends retaining him in his position provided adequate treatment is taken.

The cost of syphilis in loss of human lives and in loss of working hours from industry is tremendous. The estimated annual cost of care for cases of syphilitic nervous and mental diseases cared for in public and in private institutions is more than \$31,000,000. The cost of treatment of a case of early syphilis from infection to cure, varies between \$50 and \$600, depending on whether treatment was received by mass methods in a public clinic or whether given by a high-priced private physician. The annual cost of institutional care of the syphilitic blind has been estimated at \$10,000,000.

Recently the following suggestions were made by Surgeon General Parran in regard to syphilis control in industry. Blood tests should be done routinely in the examination of all applicants for employment, infected persons should be

employed if they accept treatment; blood tests should be made routinely on all employees and treatment should be obligatory for all syphilitics whose positions are hazardous to others; an educational program should be conducted for all employees; professional standards of privacy between the worker and the medical staff should be observed; the educational program might include prophylaxis; treatment should be provided by the medical industrial service unless it can be arranged for by the patient

In another article on the same subject R. R. Sayers¹⁹ cites cases which show the need for administrative judgment in dealing with the particular job (its requirements), and the particular syphilitic (the stage of the disease and the treatment received).

Premarital Blood Tests for Syphilis

In a circular letter to physicians from the Connecticut State Department of Health it is stated that the premarital blood test for syphilis in 1936 and 1937 has presented many important measures of control of this disease. One of the great values of the premarital blood test law has been that patients have not allowed treatment to lapse but have continued treatment as recommended by the physician. Others who did allow treatment to lapse have returned for treatment and still others have consulted their physicians for examination including a blood test for syphilis. As a result more cases have been diagnosed, as is shown by the increase in the total number of cases reported in the State, particularly for the year 1937, when 2,760 cases were reported. This is the largest number of syphilitic cases ever recorded for a single year. For the past 2 years all definitely positive blood tests on marriage license cases performed at the State Department of Health laboratories have

been followed in order to obtain certain data from the physicians concerned. From the information given by these physicians the following data were obtained:

	1936	1937	Totals
Cases of syphilis	81	112	193
Males	36	60	96
Females	45	52	97
Certificate not signed			
Communicable	44	60	104
Certificate signed Non-communicable	37	52	89

Problem of Seroresistant Syphilis

Numerous problems are presented by the patient with seroresistant syphilis, which J. E. Moore and P. Padget²⁰ summarize in three large questions:

1. What is the genesis of seroresistance?

2. What is the significance of seroresistance to the patient?

3. What is to be done about it?

In discussion of the genesis of seroresistance one might ask the additional questions: Does seroresistance indicate persistent foci of spirochetes or progressive syphilitic lesions or is the persistence of reagin in the circulating blood following antisyphilitic therapy simply a manifestation of persistent immunity? The authors state that no certain answer to these questions is possible because of lack of definite evidence, but suggest that in early syphilis seroresistance must be regarded as a manifestation of persistent foci of organisms or progressive activity but in cases of late syphilis it may result from the persistence of a well-established immunity.

The all-important question both to the physician and to the patient is, "What is the significance of seroresistance?" The authors show that in 23 per cent of the seroresistant group of early syphilis (all of whom had had adequate treat-

ment) only 5 per cent of the patients who manifested prompt serologic reversal sustained infectious relapse; similarly, neurosyphilis occurred in 31 per cent of the former but only 18 per cent of the latter. For each type of late syphilis considered the incidence of progression or relapse is essentially the same among patients who are seroresistant and those who are not.

The crux of the entire problem is, "What is to be done for the patient who manifests seroresistance?" The authors outline the aims of the treatment of syphilis early or late as: (a) The healing of lesions and the relief of symptoms, (b) the maintenance of good health and the prevention of progression or relapse, and (c) serologic reversal. Obviously, if the first and second aims can be accomplished, success or failure in the third should be a matter of complete indifference to physician and patient alike. The authors in the accompanying table summarize the steps which must be taken in the treatment of seroresistant patients with early or late syphilis.

MANAGEMENT OF SERORESISTANT SYPHILIS

In Patients with Early Syphilis

- I Examine the cerebrospinal fluid
 - (A) If reaction is positive Alter system of treatment to that for early asymptomatic neurosyphilis
 - (B) If reaction is negative
 - 1 Eliminate rest periods—treatment must be continuous
 - 2 Employ full dosage of a potent arsphenamine
 - 3 Prolong treatment for a full year of weekly injections after serologic reversal is obtained

In Patients with Late Syphilis

- I Examine the cerebrospinal fluid
- II Conduct a searching clinical study for lesions of syphilis, with particular reference to
 - (A) The cardiovascular system (including roentgenologic examination)

(B) The central nervous system.

(C) The bones

III. If abnormalities in any of these systems are discovered, plan treatment accordingly.

IV. If no abnormalities are discovered:

(A) Prolong treatment to a minimum of 2 years, continuously and with full doses.

(B) Follow the patient for the rest of his life, with, periodically, complete and searching resurveys of his clinical status.

(C) Frankly discuss and fully explain the situation to the patient and give him as much reassurance as possible

Congenital Syphilis

Congenital syphilis is classified according to E. Hoffmann²¹ into syphilis *in-nata*, *connatalis* and *postnatalis* (fetal disease, disease present at birth, and disease appearing sooner or later after birth). There has been a great decrease in the first 2 types and some decrease in the third type.

Hoffmann believes the pregnant woman is responsible for the transmission of congenital syphilis to the offspring. The fetus remains healthy until the fifth month of pregnancy. At that time there is danger of a transplacental infection with the spirochete of syphilis. It is sometimes difficult to differentiate congenital and acquired syphilis because superinfection during parturition may occur in the form of a primary lesion of the scalp. This is rare. The control of congenital syphilis depends on the early diagnosis and adequate treatment of syphilis in the pregnant woman. Serologic tests should be given before the fourth month of pregnancy. Two courses of treatment (combined concentrated courses of arsphenamine and bismuth separated by a brief interval) are sufficient to insure the delivery of a healthy child.

According to G. Sanna²² 20 per cent of pregnancies in syphilitic women lead to abortion, 20 per cent to stillbirths and 20 per cent of the children die before they reach the age of 20.

The management of congenital syphilis from the scientific, diagnostic and therapeutic standpoint is, theoretically, a comparatively simple problem, states N. R. Ingraham, Jr.²³ Every pregnant syphilitic woman should receive active and intensive treatment from the time the diagnosis of her disease is established until the time of delivery. In preventing infantile congenital syphilis, the sterilizing spirocheticidal properties of the arsphenamines are of paramount importance, the heavy metal a subsidiary aid. The treatment during pregnancy should consist, then, first of weekly injections of an arsenical and, in addition, if possible a heavy metal intramuscularly, concurrently or in alternating courses. Conservative opinion dictates that a woman once diagnosed as syphilitic should receive some active therapy in the latter part of each succeeding pregnancy, regardless of the status of the Wassermann reaction or the quantity of antecedent treatment. Exner's recent report indicating that 93 per cent of 268 representative antepartum clinics examine the blood serology of every pregnant woman for syphilis suggests that comparatively few outpatient departments at this time need to have this point emphasized. This statement, however, is not yet applicable to private obstetric practice.

If the prenatal handling of the pregnant woman has not been successful in preventing the infection of the infant, the keynote of therapy in the diseased offspring is diagnosis and treatment in early infancy. More is ordinarily to be lost by procrastination than by forcing

treatment. No syphilitic baby is too small to receive active arsenical and heavy metal therapy in appropriate dosage.

When the usual diagnostic facilities are available, it is not ordinarily considered advisable to subject all the offspring of syphilitic mothers to anti-syphilitic therapy, until they have been definitely diagnosed as being diseased. The suspected infant should have, as a minimum, a physical examination and a blood serologic check at the ages of 2 weeks, 1 month, 2 months, 3 months, 6 months, 1 year, and 2 years.

Assuming a perfect medicotherapeutic approach to the problem of congenital syphilis control, 3 social and administrative difficulties still block our full accomplishment in this field: (a) Pregnant syphilitic women do not usually report for prenatal supervision until late in their pregnancy, (b) a delay of some weeks between the initial antepartum visit and the onset of anti-syphilitic therapy is a common occurrence, and (c) congenitally syphilitic offspring frequently are not treated in *early* infancy.

In addition to maintaining treatment standards, therefore, effort should be directed, through child health and maternal welfare agencies, toward bringing the pregnant syphilitic woman and her newborn baby *sooner* under medical supervision, and toward improving clinic administration to bring a closer co-operation between obstetric and syphilis treatment agencies.

Third Generation Syphilis This is an extremely rare occurrence. According to Stokes, "The rub comes in the establishing of the prenatal as distinguished from the possibly acquired syphilis of the second generation mother." J. C. Clark²⁴ has reported apparently clear-cut cases of congenital syphilis in the second and third generations.

The Infectiousness of Semen of Patients with Late Syphilis

An important question in the control of syphilis is the part played in the propagation of the infection by the male with untreated or insufficiently treated late syphilis. That the semen of such individuals might be infectious was first suggested by Astruc in 1740. In an experimental study of the infectiousness of the semen in late syphilis, J. E. Kemp²⁵ obtained 15 specimens from 15 different individuals all with syphilis of 4 years' duration or more and inoculated rabbits intratesticularly. These inoculations were all negative as were popliteal lymph node transfers of the originally inoculated animals. Six of the 15 patients were untreated. In the remaining 9 patients treatment antedated the examination of the semen by at least 4 years.

Five of the 15 specimens of semen from syphilitic individuals were collected aseptically and portions of each inoculated into the posterior chamber of 1 eye of each of the 2 rabbits which received the intratesticular inoculation. The control groups comprised rabbits inoculated in the posterior chamber with the semen collected aseptically from 4 nonsyphilitic individuals and rabbits inoculated in the same manner with material collected under cleanly but not aseptic conditions from 4 nonsyphilitic individuals. Except that the ophthalmia developed by the animals inoculated with the semen that was not collected aseptically was somewhat more severe, there was very little difference in the appearance of the eyes of the animals inoculated with the semen of syphilitic and nonsyphilitic individuals.

In an attempt to determine the reason for the belief that semen is more infectious than the other body fluids of

individuals with late syphilis, it was found:

1. That this belief originated in the pre-Wassermann era as an explanation of the apparent immunity to syphilis of the mothers of congenitally syphilitic children.

2. After the discovery of the treponeme, attempts to demonstrate its presence in the semen were unsuccessful in the majority of instances. Nevertheless, belief in the infectiousness of semen persists, mainly for 2 reasons: (a) The frequency with which experimental animals, inoculated elsewhere with syphilis, develop metastatic testicular lesions. This experimental observation has been considered sufficiently significant to justify the assumption of the presence of treponemes in the semen. (b) The finding of an interstitial fibrosis of the testes in a large proportion of patients with late syphilis who come to necropsy. The demonstration of treponemes by silver staining in certain such tests has been taken as proof that this type of testicular fibrosis is characteristic of syphilis. This assumption, although as yet unproved, has been considered sufficient to permit the further assumption that the semen of patients with late syphilis may harbor the treponeme.

3. A review of the available literature shows that, including our 15 cases, the semen of 144 individuals with syphilis has been investigated for the presence of treponemes either by dark-field examination, silver staining, animal inoculation, or by a combination of one or more of these methods. In 14, or 9.7 per cent, of these 144 individuals treponemes were demonstrated by 1 or more of the several methods employed. In 119 instances it was possible to determine with a certain degree of accuracy the duration of the syphilitic infection at the time the semen was examined. Sixty-seven indi-

viduals had early syphilis (syphilis of 4 years' duration or less) and 52 had syphilis of more than 4 years' duration. Treponemes were demonstrated in the semen of 13 of the former group, or in 19.4 per cent. The majority of this group had untreated florid secondary syphilis or infectious mucocutaneous relapses. In contrast, in only 1 instance (1.9 per cent) were treponemes demonstrated in the semen of the 52 individuals with late syphilis.

In conclusion the author states that a review of all the available experimental studies shows that treponemes have been demonstrated in the semen of patients with early syphilis in about the same frequency with which they have been demonstrated in the other body fluids of patients with early syphilis. No adequate reason for persistence in the belief of the infectiousness of the semen of patients with late syphilis was found, since there is little evidence that any of the body fluids in this stage of the disease are frequently infectious.

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OPHTHALMOLOGY

By CONRAD BERENS, M.D., and JOSHUA ZUCKERMAN, M.D.

CYST OF ANTERIOR CHAMBER

Treatment — Roentgen radiation for the treatment of an epithelial cyst of the anterior chamber which developed post-operatively is reported by C. A. Perera.¹ Five doses of 150 roentgens were administered at weekly intervals until a total of 750 R. had been given, using 200 kv., 0.5 mm copper filtration and 50 cm. T.S.D. In 2 months, when the cyst reformed, a second series of 5 treatments was administered, using 108 kv. and 3 mm aluminum, with 25 cm. T.S.D. The cyst disappeared completely. The literature and experimental investigations reveal that hypotony which usually results from incarceration of the iris or of the capsule of the lens following cataract extraction is an important factor in epithelialization of the anterior chamber. Experimental introduction of a flap of superficial corneal tissue into the anterior chamber of rabbits revealed that the epithelium which proliferated immediately after the operation, gradually degenerated and disappeared without epithelialization of the anterior chamber.

Roentgen radiation for the treatment of a cyst of the anterior chamber is also recommended by L. Wittels.² In this case the cyst developed 14 years after a gunshot injury. The tension was normal and the vision 3/36. After 3 x-ray treatments of 100 R. each at a distance of 34 cm. with a 0.5 mm copper and a 10 mm aluminum filter, the size of the cyst was reduced, the pupil became clear and vision was restored to 6/12.

SUPRATENTORIAL BRAIN TUMOR

Localization — C. A. Elsberg³ believes that visual tests are clinically valuable in localizing supratentorial tumors of the brain. Examination of 19 proved cases of supratentorial tumor revealed that, in lesions of 1 hemisphere, the time required for dark adaptation of the eye of the opposite side is longer than for that of the homolateral side; and that if the tumor is located in or near the frontal lobe the time required for dark adaptation of the eye on the same side after exposure to a flickering light is longer than that after a continuous light

SUBCHOROIDAL HEMORRHAGE

Treatment — *Posterior sclerotomy* for the treatment of subchoroidal expulsive hemorrhage resulting from surgical or traumatic penetrating wounds of the eyeball is advocated by D. Vail.⁴ He points out that, according to Samuels, the blood comes from rupture of 1 of the 2 long posterior ciliary arteries at its point of entry into the perichoroidal space. The choroid may be pushed forward by the blood, other blood vessels in the perichoroidal space may be torn, the choroid may be ruptured and the intraocular contents may be expelled. Vail reports 2 cases and concludes that sclerotomy may save the eye in threatened expulsive subchoroidal hemorrhage resulting from operation. In expulsive hemorrhage rup-

(383)

ture of the choroid occurs and the eye is always lost; in nonexpulsive hemorrhage no rupture of the choroid occurs. In serous detachment of the choroid following operation, the eyeball is soft; in nonexpulsive subchoroidal hemorrhage, the eyeball is hard. Examination of laboratory material indicates that nonexpulsive subchoroidal hemorrhage occurs more frequently after the trephine and Lagrange operations than after simple iridectomies.

CONJUNCTIVA

Burns of Conjunctiva

Treatment—The use of *mucous membrane grafts* in cases of burns of the conjunctiva has been advocated by (1) Thies.⁵ Transplants of mucous membrane are taken from the lips and applied to the burned area of the conjunctiva as soon as possible after the accident.

Bacillus Coli Conjunctivitis

Treatment—From his experiments with bacillus coli in rabbits' eyes, W. Johnston⁶ concludes that traumatism seems necessary in order to enable the colon bacillus to infect the conjunctiva and that this bacillus is readily destroyed by preparation of mercury, *e g.*, 1 per cent *yellow oxide of mercury*, solutions of 1:2000 of *metaphen* or of 1:8000 of *oxycyanide of mercury*.

Gonorrheal Conjunctivitis

Treatment—L. J. Fernandez and R. F. Fernandez⁷ treated 8 cases of gonorrheal ophthalmia in adults who had only 1 eye affected. In the first case, 40 grains (2.6 Gm.) of *sulfanilamide* were given daily for the first 3 days in 4 doses of 10 grains (0.65 Gm.) at 8 A. M., 1 P. M., 6 P. M., and 11 P. M. On the fourth day a daily dose was given of 30

grains (1.95 Gm.), administering 10 grains (0.65 Gm.) at 8 A. M., 3 P. M., and 10 P. M., in addition to local treatment and 1¼ drams (5 cc.) of milk intramuscularly. On the fourth day after 2 drams (7.80 Gm.) of the drug had been administered, the infection was checked. On the sixth day, because gonococci were still present in the conjunctival scrapings, the dose was increased to 40 grains (2.6 Gm.) daily. For the next 3 days gonococci were absent in the smear and culture. In the next 3 cases in addition to the sulfanilamide only mild local treatment and no milk was employed. The next 2 cases were effectively treated with sulfanilamide and irrigations with normal saline solution. In the last 2 cases, sulfanilamide was administered without local treatment and the results were as remarkable as in the previous cases, indicating that sulfanilamide alone is effective in combating the disease. They conclude that all patients to whom sulfanilamide was administered recovered in a shorter period of time than those treated by other accepted forms of treatment. Smaller doses are recommended for patients with renal insufficiency because sulfanilamide is excreted slowly.

Staphylococcic Conjunctivitis

C. S. O'Brien and J. H. Allen⁸ direct attention to the staphylococcus as a common cause of conjunctivitis. This condition is usually characterized by bilateral chronic blepharoconjunctivitis, meibomianitis, excoriations, crusts, and scales and sometimes is associated with superficial punctate keratitis. Congestion and thickening of the caruncle and semilunar fold are almost pathognomonic. Lacrimation is pronounced, discharge scanty and marginal ulcers and mild iritis may develop. In infants, staphylococcus conjunctivitis has an acute onset, is self-limited, and may develop at any

time after birth. In adults the disease requires prolonged treatment consisting of local therapy and immunization. The contents of the meibomian glands are **expressed repeatedly, 2 per cent silver-nitrate solution** is applied to the conjunctiva and local antiseptics are instilled at home. Immunization is attempted with *staphylococcus toxoid*, *autogenous vaccine* or *staphylococcus antitoxin*. Treatment with silver nitrate should not be continued over too long a period.

Lupus of the Conjunctiva

Treatment—A case of lupus erythematosus of the conjunctiva, associated with spots of erythema on the face, is reported by P. W. Montgomery.⁹ The lesions in the conjunctiva and in the skin disappeared after treatment with **sodium gold thiosulfate**.

Preoperative Sterilization of Conjunctiva

From his experience in 126 cases, K. F. Robitashvili¹⁰ demonstrated that 2 per cent **yellow oxide of mercury** is the most effective drug for preoperative sterilization of the conjunctival sac.

Trachoma

Treatment—Satisfactory results in the treatment of the complications of trachoma by subconjunctival **autohemotherapy** have been obtained by E. S. Martinez.¹¹

The injection is administered in the upper *cul-de-sac*. Autohemotherapy is effective in the treatment of torpid ulcers, pannus and hypopyon resulting from pneumococcus.

Antimony Tartrate—V. Derkac¹² treated 50 cases of trachoma by means of intravenous injections of freshly prepared sterile solution of **antimony tar-**

trate in addition to the usual local treatment with **copper stick**. From 2 to 3 cc. of a 1 per cent solution were administered every second day, in a series of 10 doses, with intermissions of from 10 to 14 days. Pannus and ulcers of the cornea disappeared and ptosis and blepharospasm were relieved.

Traumatic Conjunctivitis

The fact that traumatic lesions of the conjunctiva are common in industrial cases is stressed by Vila Ortiz.¹³ An abscess may form from a subconjunctival foreign body, and interstitial keratitis from a subconjunctival hemorrhage and an acute infectious conjunctivitis may develop from direct inoculation.

He advocates examination of the conjunctival secretion in every case of acute conjunctivitis following trauma, not only for therapeutic but also for medico-legal purposes. He tabulates the periods of incubation as follows. Gonococcus, 3 to 5 days, pneumococcus, 6 to 12 days, diplobacillus, 3 days, Koch Weeks bacillus, 1 to 2 days, measles, 8 to 12 days, diphtheria, 1 to 5 days, scarlet fever, 3 to 5 days, and trachoma, 7 to 15 days.

Caustic Burns of Conjunctiva and Cornea

Treatment—It is stated by W. B. Hubbard¹⁴ that caustic burns of the eye should be treated by **irrigation with water** and **weak acids**. Moreover, an alkaline neutralizing fluid should be avoided. Employment of **tannic acid** and other antiseptics (**methyl rosaniline** and **silver nitrate**) is preferred.

CORNEA

Keratoplasty—Grafts—The results of clinical and microscopic studies of corneal grafts employed in keratoplasty are discussed by R. Castroviejo.¹⁵ A trans-

parent graft retains its individuality and preserves its own cellular elements. Opacification and clouding of the graft may result from poor coaptation between the margins of the graft and that of the cornea of the host, vascularization of the graft, incarceration of the intraocular structures, or postoperative infection. Grafts entirely surrounded by dense scar tissue usually become opaque. Employment of conjunctival flaps is less satisfactory than suturing of the cornea.

Infection of Cornea

Treatment—M. I. Fradkin, H. P. Beketovskii, and L. S. Levin¹⁶ recommend the use of *lysozyme* in cases of postoperative infections of the eye. They applied it on a cotton pledget directly to the wound in 10 cases of infection following cataract extraction. They have also found it effective by instillation in cases of perforating wounds of the cornea.

Keratitis

Diagnosis—A. B. Katznelson¹⁷ is of the opinion that fascicular keratitis is a tuberculous allergic manifestation.

Treatment—Eleven cases of dendritic keratitis and 1 of herpes zoster of the cornea were successfully treated by E. Schinger¹⁸ by introducing into the conjunctival sac twice a day an ointment containing 2 per cent *quinine bisulfate*.

Superficial Punctate Keratitis—Twelve cases of superficial punctate keratitis were treated by A. Cowan and T. H. Cowan¹⁹ with a solution of 1 per cent *potassium iodide* containing 1 or 2 minims of *compound solution of iodine*. The drops were instilled 3 times a day, and *packs of Pregl solution* were repeatedly applied to the conjunctiva for 10 minutes at a time. As a result of this treatment, rapid disappearance of the lesions in the cornea took place or recurrence was delayed.

Syphilitic Keratitis

Late prenatal syphilis with special reference to the prevention and treatment of interstitial keratitis are discussed by H. N. Cole and others.²⁰ Clinical results are better if treatment is instituted before the age of 15 years. They recommend 16 injections or rubs of *mercury*. Continuous therapy for prenatal syphilis is the best prophylactic measure. *Iodides* are valuable adjuncts for the treatment of chronic recurrent interstitial keratitis.

Cornea Ulcers

Treatment—Vitamin Therapy—From his experiments with animals, E. Federici²¹ concludes that *cod-liver oil* (vitamins A and D) in solution or as a 10 to 50 per cent ointment, is valuable in the treatment of ulcers of the cornea.

Jan Vanysek²² reports that the oral administration of *carotene* (vitamin A) stimulates regeneration of corneal tissue.

Lacrimal Gland Extract—Good results have been obtained in marginal, dendritic and trachomatous ulcer by the instillation every 2 hours of 5 per cent extract of *bovine lacrimal gland* in a solution chemically identical with human tears, according to W. H. Melanowski.²³

CYCLOPLEGIA

The use of *benzedrine* in cycloplegia is discussed by S. J. Beach and W. R. McAdams.²⁴ They recommend instillation of a solution of 5 per cent *homatropine* or 1 per cent *atropine* followed in 2 or 3 minutes by instillation of a solution of 1 per cent benzedrine sulfate, which in turn is followed, after several minutes, by a second instillation of the homatropine (or atropine). Homatropine-benzedrine cycloplegia reaches its peak in from 50 to 70 minutes and may last from 5 to 7 hours. Atropine-ben-

zedrine cycloplegia reaches its height in an hour, and usually lasts 1 day but may last from 2 to 4 days. By comparing the depth of cycloplegia obtained by the conventional use of homatropine or atropine respectively with that obtained by the benzedrine method, they found that the average gain by the use of conventional homatropine was 0.035 diopter, and that the average gain by use of conventional atropine was 0.23 diopter. The main advantage in the use of benzedrine cycloplegia is the rapidity of disappearance of the cycloplegic effect.

DISSEMINATED SCLEROSIS

Treatment—For the treatment of disseminated sclerosis, G. R. Kamman²⁵ recommends *quinine* by mouth, *sweats*, *high-vitamin diet*, intramuscular injections of *sodium cacodylate* and *rest in bed*. If this treatment does not result in improvement, *foreign protein therapy* should be tried

BIRTH INJURIES

R. I. Lloyd²⁶ states that most birth injuries of the cornea result from compression of the eyeball between the obstetrical forceps and the roof of the orbit. Descemet's membrane may present tears directed vertically or horizontally in a parallel direction. If these do not heal, aqueous enters the cornea and permanent clouding results. Descemet's membrane may be stripped and separated into flat strips retaining terminal attachments near the aqueous. Keratoglobus, keratoconus, high degrees of astigmatism with myopia and amblyopia may result. Lloyd reports 6 cases illustrating strands of glassy material, persistent pupillary membrane, clouding of the cornea, microphthalmos, persistent hyaloid artery and a glass membrane which developed

during tuberculous uveitis. He points out that the left eye is usually involved because left occipitoanterior presentations preponderate; that 1 of his cases which presented remnants of the pupillary membrane attached to the posterior corneal surface occurred in a microphthalmic eye; pigment on the posterior surface of the cornea and on the anterior surface of the lens with remains extending from the iris to the cornea result from late separation of the cornea from the tunica vasculosa lentis which in turn results from delayed formation of the anterior chamber.

EYE

Metastatic Carcinoma

A case of metastatic carcinoma of the eye is reported by W. Kreibitz.²⁷ A patient, 44 years of age, in apparently perfect health, presented nodular iridocyclitis for several weeks associated with recurrent hemorrhages into the anterior chamber. The fundus was normal. It was discovered that a carcinoma of the bronchus was present. The nodules in the iris grew rapidly and metastatic lesions occurred in the ribs and scapula.

Endocrine Dysfunction of Eye

The ocular manifestations of dysfunction of the thyroid, parathyroid, pituitary and adrenal glands, and of the pancreas and the gonads are discussed by A. N. Lemome.²⁸ Certain forms of glaucoma, cataract, myopia, and keratoconus apparently are associated with endocrine dysfunction. In hypothyroidism edema of the retina around the disc and the macula and elevation of the disc may be found.

Fever Therapy (Hyperpyrexia) in Eye Conditions

W. W. Weeks and S. A. Morris²⁹ treated a series of 16 eye cases by means

of general hyperpyrexia induced with the inductotherm in addition to the usual local treatment. After a complete physical examination including chest x-ray and laboratory investigation, a high caloric diet, and 4000 cc. of 0.6 per cent saline is administered by mouth the day preceding treatment. On the day of inducing fever a soapsuds enema and a sedative are administered and no breakfast is allowed. Pulse, respirations, and rectal temperature are taken every 5 minutes and the treatment is discontinued if the temperature fluctuates irregularly, and if the pulse goes above 160 and if respirations rise above 45 per minute or become irregular. This series consisted of 3 cases of gonorrheal ophthalmia, 4 cases of iritis of probable gonococcal origin, 3 cases of iritis of unknown etiology, 1 case of superficial punctate keratitis, 1 case of scleritis and iritis, 1 case of uveitis; 1 case of trachoma with secondary purulent staphylococcus conjunctivitis, and 2 cases of interstitial keratitis. They conclude that physical fever therapy is valuable in the ocular complications of gonorrhea, in iritis, in superficial punctate keratitis, and in scleritis, but is of little or no value in cases of trachoma, syphilitic uveitis, and interstitial keratitis.

Malaria

A. E. Goldfeder³⁰ states that bilateral anesthesia or hypoaesthesia of the cornea is suggestive of malarial infection of the eye and that a greenish-gray or bluish-gray appearance of the peripapillary or macular region is pathognomonic of malaria.

Irradiation of Eye

M. Cutler, H. L. Jaffe and A. Grossman³¹ discuss not only the therapeutic but also the injurious effects of irradiation

of the eye and suggest the use of a protective device to prevent injury. Complications can be avoided if fundamental principles of irradiation therapy, careful technic and the use of adequate protective devices are observed. They point out that roentgen rays and radium are similar in their action upon the eye. The reaction of the eyelids to radiation is characterized by erythema, edema and desquamation. The reaction of the conjunctiva usually occurs 3 weeks after treatment but may appear earlier and consist of edema, hyperemia, and epiphora; conjunctivitis associated with photophobia and tearing may occasionally result. The reaction of the cornea is usually slight but a temporary keratitis may result. The reaction of the iris, lens and the tissues of the posterior segment is negligible if proper irradiation with suitable protection is performed. In cases of extensive unoperable lesions irradiation is indicated even if sacrifice of the eye becomes necessary. Among some of the complications of irradiation therapy are: Loss of cilia, radium necrosis and scarring of the eyelids, obliteration of the fornices, ectropion, dryness of the conjunctiva and cornea resulting from destruction of the lacrimal glands, stenosis of the lacrimal puncta, ulceration of the cornea, keratitis and occasional radionecrosis of the cornea with perforation of the eyeball, cataract formation particularly in infants and children (following x-ray rather than radium therapy) and even in the untreated eye if it is not properly protected, and detachment of the retina. The authors recommend the use of a prothesis consisting of a layer of lead 1.2 mm. thick, covered by a sheet of nickel between which a thin coat of cadmium is interposed. This protective device is only 1.3 mm. thick and weighs only 10 Gm.

Pain in Eye

Treatment—The application of *carbolic acid* to the sphenopalatine ganglion in cases of neuralgia of the head and face is recommended by R. Thurel.³² A cotton tampon saturated with carbolic acid is applied to the mucous membrane behind the middle turbinate. Frequent applications are made for an hour and repeated 3 times at intervals of several days. The carbolic acid penetrates the mucous membrane, and enters the pterygomaxillary fossa to affect the sphenopalatine ganglion. The treatment is recommended for the relief of pain in cases of episcleritis, subacute and chronic glaucoma, neuroparalytic keratitis, iritis, vasomotor crises, photophobia and retrobulbar neuritis.

Senile Changes in Eye

In a discussion of senile changes and degenerations of the human eye, B. Rones³³ points out that it is important to distinguish senile from pathologic lesions. Senility may be manifested in the eye as follows: (*a*) In the eyelids by "crow's feet," resulting from thinning of the skin and disappearance of fat and muscle tissue beneath the skin, folds and pouches resulting from the disappearance of the elastic fibers, ectropion, entropion, hyperkeratosis, and xanthelasma, (*b*) in the conjunctiva by pinguecula, and pigmentation of the conjunctiva and limbus, (*c*) in the cornea by arcus senilis, pigment on the posterior surface of the cornea, senile marginal atrophy with ectasia and rupture of Descemet's membrane, and bilateral band-shaped opacity of the cornea, (*d*) in the sclera by fatty infiltration, deposition of granules of calcium salts, degeneration of the elastic tissue, sclerosis of the arteries, areas of softening and scleromalacia perforans; (*e*) in the pectinate ligament by thickening and sclerosis of the fibers; (*f*) in the

iris by the disappearance of the pigment epithelium at the pupillary margin producing an ill-defined border, senile miosis, rigidity of the pupil, thinning of the iris, hyaline degeneration of the fibers of the dilator muscle, and sclerosis of the blood vessels, and (*g*) in the ciliary body by thinning and deposition of fat in the fibers and of calcium granules between the fibers, more numerous branching of the ciliary processes, resulting in an increased volume. Rones concludes that during advancing years the vascular changes result in impaired nutrition with deposition of fat globules, and in proliferative and degenerative changes.

Syphilis of Eye

Treatment—A discussion of the treatment of syphilis of the eye is presented by D. Kravitz.³⁴ A patch test for sensitivity or allergy to arsenic is advisable to avoid the Herxheimer reaction. The most suitable time for treatment of syphilis is in its early phase. At this time *arsphenamine* is superior to neoarsphenamine. At first *arsenic* and the *heavy metals* combined are indicated but after 3 or 4 weeks alternate treatment should be administered. Continuous, not intermittent, courses should be continued for 1 year after spinal fluid and blood Wassermann tests are negative. All arsenicals, except *tryparsamide*, are usually contraindicated in cases in which the kidneys are impaired, in debility, and in advanced cardiovascular disease. Tryparsamide is a pentavalent arsenical, less toxic than any other arsenical and less likely to produce a Herxheimer reaction. Unlike the trivalent arsenicals (arsphenamine or neoarsphenamine), tryparsamide is particularly valuable in the treatment of syphilis of the central nervous system and in cardiovascular syphilis when it is associated with cerebral syphilis. It is

advisable that the spinal fluid should be tested in early syphilis; if the result is negative the test should be repeated in a year. **Bismuth** is particularly useful for periostitis of the orbital bones. It is safe in cases associated with disease of the liver or kidneys in which arsenic and mercury are contraindicated. Arsenic is better tolerated by children than by adults. From 10 to 16 weeks of treatment with arsenic is usually indicated. If improvement does not result, **bismuth and iodides** should be administered. Moore is of the opinion that sulfarsphenamine is best for the treatment of early congenital syphilis. **Subdural injections of arsphenamine** are effective in the treatment of syphilitic optic atrophies except when they follow optic neuritis. **Fever therapy** is valuable in cases of optic atrophy associated with paresis. Cure may be interpreted as eradication of all treponemas, disappearance of all signs and symptoms and negative complement-fixation of spinal fluid and blood.

Blood Transfusion in Eye Conditions

The use of **blood transfusion** in ophthalmology is advocated by W. G. Frey.³⁵ He recommends its use as whole blood, or as citrated blood, in cases of hemophilia, hemorrhages in the retina, eclampsia, amaurosis following loss of blood, inflammatory lesions of the eye, vitreous opacities and turbidity of the vitreous in sympathetic ophthalmia, and anterior uveitis. In his experience blood transfusion has also been effective in trophic lesions, *e g*, lattice keratitis and dendritic keratitis. He concludes that repeated transfusions constitute a valuable nonspecific therapeutic agent in inflammatory trophic lesions of the eye.

Tuberculosis

Diagnosis — According to A. C. Woods³⁶ the diagnosis of tuberculosis of

the eye is based on the character and course of the lesion, the tuberculous status of the patient, the reaction to tuberculin and the exclusion of other etiologic factors. The uveal tract is particularly susceptible to tuberculosis, but any structure of the eye may be affected. Tuberculosis may present itself in 1 of 3 clinical manifestations: (a) Characteristic lesions, *e g*, nodular iritis, tuberculomas of the anterior or posterior uvea and miliary tubercles of the choroid, (b) lesions of the cornea, iris, or choroid, characterized by self-limitation of the attack, a tendency to recurrence, or (c) a group of exudative caseating lesions particularly of the uvea which may destroy the eye. Tuberculin reactions are significant only when strongly positive. The value of tuberculin is greatest when administered over a long period of time on the concept of desensitization.

Treatment—A. Musial and M. Lauterstein³⁷ discuss the therapy of tuberculosis of the eye with **tuberculin**. Their analysis of 400 cases treated with tuberculin revealed that tuberculosis occurs more frequently in men between 20 and 50 years of age, particularly in agricultural populations. Keratoconjunctivitis, iridocyclitis, and choroidoretinitis occurred most frequently. Old tuberculin was more effective than tebeptem. Of the 400 cases, 220 were cured, 155 improved, and 25 unimproved.

A. C. Woods and M. E. Randolph³⁸ treated 175 cases of tuberculosis of the eye with tuberculin. They conclude that the desensitization theory of the action of tuberculin is correct, and that tuberculin should be administered for a minimum of 2 years and should be discontinued only if the skin has become almost totally nonreactive and the lesion in the eye has become quiet for a period of a year or longer. Cutaneous sensitivity should be tested at 3-month periods.

and tuberculin therapy again instituted if cutaneous sensitivity recurs.

Keratomalacia—Vitamin Deficiency

According to J. Vanysek³⁹ all cases of keratomalacia studied in the Brno Clinic resulted from deficiency of vitamin A and developed xerophthalmia. Administration of *carotene* resulted in rapid improvement.

War Gases

Treatment—V. Clemmesen⁴⁰ suggests methods of treatment and protection of the eyes against gases employed in war. The gases may be divided according to their actions, as follows: (a) Tear gas (chloracetophenon); for which a solution of 2 per cent *sodium bicarbonate* or a solution of 0.4 per cent *sulfite* in water and glycerine 1 part to 4 is of assistance, (b) sneezing gas (arsenic), for which *irrigation* of the eye with a mild *alkaline solution* is effective; (c) gases affecting the lungs (phosgene, diphosgene, and nitrochloroform, the green gases); for which *boric acid solution* and *mild alkaline solutions* and ointments are of assistance, and (d) gases irritating the skin (mustard gas, yellow gas); for which protection is afforded by rubbing *chloride of lime* (calcium hypochlorite) into the skin of the eyelids or by *wearing gas masks*. Mustard gas produces the severest lesions of all, e. g., conjunctivitis, opacities and ulcerations of the cornea, perforation and blindness. *Alkaline solutions* and ointments containing *calcium carbonate* and lime water are recommended.

EYELID CHALAZION

A. V. Lotin⁴¹ reports a case of recurrent chalazion which on microscopic examination proved to be a basal-cell carcinoma.

EXOPHTHALMOS

Chloroma of Orbit

A case of exophthalmos which resulted from a chloroma of the orbit occurring in a boy 4 years of age is reported by A. D. Frost.⁴² This type of tumor is part of a myelogenous leukemia, diagnosis of which is made from the blood picture and the presence of tumor masses containing embryonic myeloid cells. *Roentgen irradiation* is the most satisfactory form of treatment, and *blood transfusions* are of value. In suspicious cases, not only a routine blood count but also a complete blood study should be made, using supravital staining method.

Unilateral Exophthalmos

Etiology—An analysis of a series of 71 consecutive cases of unilateral exophthalmos in order to determine the etiologic factors is presented by M. E. Randolph.⁴³ He classifies the causes as follows: (a) Malignant tumors, which may be primary, orbital, metastatic or extensions into the orbit; (b) benign tumors, which may be primary, orbital, noninflammatory extensions or mucocoeles; (c) inflammations of the orbit; (d) traumatism of the orbit, and (e) exophthalmos resulting from unknown causes. Diagnosis was confirmed by biopsy in 42 cases. A clinical diagnosis was made in 29 cases based on the result of irradiation, antisiphilitic therapy or on the discovery of a primary lesion elsewhere in the body. In the group of malignant tumors there were 15 primary tumors of the orbit, 10 sarcomas, 2 dural endotheliomas, 1 mixed tumor of the lacrimal gland, and 1 neuroblastoma of the optic nerve; 6 patients had metastatic tumors of the orbit, 3 of which were from the breast, 1 from a sarcoma from the femur, 1 from a myeloma of the humerus.

and 1 from a neuroblastoma of the adrenal; 10 patients presented tumors involving the orbit by direct extension, 5 were basal-cell carcinomas arising from the eyelid and inner canthus, the remainder were sarcomatous or carcinomatous extensions from the sinuses or nose. In the group of 8 benign primary tumors of the orbit, 5 were angiomas, 1 a sebaceous cyst, 1 a recurrent fibroma, and 1 a recurrent lymphoma, of the 4 noninflammatory conditions involving the orbit by extension, 1 was an angioma arising from the right antrum, 1 was an ossified fibroma of the frontal bone, 1 was a case of pulsating exophthalmos improved by ligation of the left internal carotid artery and 1 was an encephalocele; of the 5 cases of mucocele of the orbit, extension arose from the sinuses. In the group of 10 inflammations of the orbit, 4 were gummas. In 4 patients the inflammatory nature of the process was not recognized until operation was performed. There were 3 cases of cellulitis of the orbit arising from sinus infection. In the group of 3 cases of trauma of the orbit, retrobulbar hemorrhage produced unilateral exophthalmos. In the group of 9 cases of proptosis resulting from unknown causes, 6 were diagnosed as tumor of the orbit, but the diagnosis was not confirmed. Randolph concludes that sarcomas are the most common of the primary tumors of the orbit and the most frequent cause of unilateral exophthalmos in children, angiomas are the most frequent of the benign primary tumors of the orbit, and that metastatic tumors of the orbit are rare.

INTRAOCCULAR FOREIGN BODY

Treatment—From an analysis of 300 cases of intraocular foreign bodies, W. H. Stokes⁴⁴ concludes that the presence

of a retained foreign body in the eyeball does not necessarily indicate enucleation because such foreign bodies are often well tolerated in the anterior chamber and in the posterior coats of the eye. A foreign body was retained in 101 cases for a period of from 1 month to 35 years. Of these, 60 developed total permanent loss of vision, while 22 cases (in 13 of which the foreign body was not removed) retained good vision. Retention of a foreign body in the vitreous usually results in loss of vision. Sympathetic ophthalmia did not occur in any case of retained foreign body but did occur in 2 cases following the extraction of the foreign body. Foreign bodies in the anterior segment should be removed by the anterior route, foreign bodies in the posterior segment through the sclera after the application of diathermy around the wound.

GLAUCOMA

Treatment—*Opticociliary neurotomy* in cases of painful absolute glaucoma is recommended by R. F. Perena⁴⁵. The operation is also valuable in cases of phthisis bulbi when a prosthesis is to be worn, provided the danger of sympathetic ophthalmia is absent.

Goniotomy—The utilization of the binocular corneal microscope to obtain magnification is recommended by O. Barkan⁴⁶ for opening Schlemm's canal in cases of chronic simple glaucoma. His technic is as follows. A helmet is worn to which is attached a binocular corneal microscope. The microscope is steadied with the left hand, the little finger of which rests on the patient's head. A surgical contact glass is applied to the eye and steadied by a double-pronged probe which fits into 2 depressions on its surface. A narrow beam of light transilluminates the limbus and the angle of

the anterior chamber. The knife held in the right hand is guided across the chamber by direct vision through the contact glass until it reaches the magnified angle of the anterior chamber. The point of the knife is inserted exactly at that portion of the trabeculum which covers Schlemm's canal and an incision, a few millimeters long, is made along this line.

Incarceration of Iris—From their results in 22 chronic, 13 acute and 14 complicated cases of glaucoma, L. Weekers and J. Fanchamps⁴⁷ conclude that operations for glaucoma in which the iris is incarcerated are the most effective

IRIS

Iridocyclitis

H. Lagrange and J. Goulesque⁴⁸ report 3 cases of iridocyclitis associated with focal infection. Although 2 were syphilitic, specific therapy did not improve the condition. The iridocyclitis improved after operation on the nasal accessory sinuses which were diseased in all 3 cases. The focus of infection in the sinuses seems to act as a sensitizing agent producing an allergic reaction in the reticuloendothelial structure of the uvea.

Prolapse of Iris

Treatment—*Simple excision* of traumatic prolapse of the iris without making a conjunctival flap is advocated by J. Kolacny⁴⁹. The advantages are that corneal astigmatism is avoided, healing is more rapid, and the cosmetic effect is better.

LACRIMAL DUCT

Stenosis

Treatment—Sven Larsson⁵⁰ performs intranasal surgery for the treatment of congenital atresia of the nasolacrimal duct. He recommends removal

of the anterior portion of the inferior turbinate, and incision of the nasal mucous membrane over a probe inserted through the lacrimal sac.

Lacrimal Punctum—Eversion

Treatment—*Excision of a rhomboidal strip of conjunctiva* from the nasal half of the border of the eyelid for the correction of eversion of the lower lacrimal punctum is advocated by P. E. Tikhomirov.⁵¹

Lacrimal Sac—Visualization With Lipiodol

According to E. W. Spackman,⁵² the injection of lipiodol followed by roentgenographic examination assists in the detection of pathologic conditions of the lacrimal apparatus. This method is particularly helpful in cases of: (a) Congenital deformities, (b) inflammatory processes in the wall of the orbit or of the lacrimal bone, (c) atresia of the duct, (d) obstructions of the sac, dilatations, adhesions, contractions, pressure and distortion of the sac, or of the nasolacrimal duct, (e) fistulas, (f) malignancy, and (g) deformities resulting from cicatrization of local wounds and traumatic rupture. Spackman recommends slow injection of $1\frac{1}{2}$ to 1 cc of a mixture of equal parts of lipiodol and sterile olive oil into the lower punctum.

LENS

Dinitrophenol Cataracts

Etiology—H. Barkan and J. W. Bettman⁵³ report a case of so-called dinitrophenol cataracts which developed without the ingestion of dinitrophenol. These cataracts developed in both eyes of a woman, 23 years of age, who had taken "Slendrets" for a week. History revealed that she had taken other drugs, too (ergot about 2 years before and qui-

nine about 3 months before being examined) and had had some febrile disease.

Cataract

Prevention—Vitamins—According to S. R. Gifford,⁵⁴ there is no known nonsurgical treatment that will cure cataract once it has formed but vitamins liberally used may possibly prevent its formation or arrest its progress.

Water—According to E. Jackson,⁵⁵ daily ingestion of water in large amounts arrests the development of lenticular opacities in elderly persons.

Treatment—M. J. Blaess⁵⁶ reports a series of 37 cases of soft cataract which were aspirated by oral suction after discussion of the anterior capsule had been performed several days previously.

Vitamin C—Seven cases were treated for senile cataracts by V. Derkac⁵⁷ by the local application of vitamin C, only 2 of which were treated over a long period of time. Improved vision resulted from instillation or subconjunctival injection of vitamin C. Severe reaction followed intraocular injection.

MUSCLES

Heterophoria

In a discussion of the relationship of heterophoria to divergence and convergence, F. H. Haessler⁵⁸ concludes that the degree of exophoria or esophoria is not determined by a balance between divergence and convergence as expressed in the usual clinical measurements. His conclusions are based on a series of 1000 cases.

Divergence Insufficiency—According to A. DeH. Prangen and F. L. P. Koch⁵⁹ divergence insufficiency is responsible for many cases of asthenopia, particularly in the use of the eyes for near vision. The usual findings in di-

vergence insufficiency are homonymous diplopia in all fields of distant vision but not of near vision, normal excursion movements, weakness or absence of divergence power, esophoria for distance and near but greater for distance while the convergence may be normal or greater than normal. From their observation of 4 cases of divergence paralysis they conclude that a cerebral center exists for control of divergence. They found that prisms base out incorporated in the correcting lenses to correct the horizontal imbalance and vertical prisms to correct the vertical imbalance are helpful.

Limitation of Motion of Muscles

Tenon's Capsule Transplant—An operation for the correction of post-operative deviation and limitation of motion of the eyeball resulting from undesired adhesions between the muscle and the sclera has been devised by C. Berens.⁶⁰ Reformation of adhesions is prevented by inserting a piece of Tenon's capsule, about 10 mm. square, which has been excised and reversed so that its smooth scleral surface lies under the muscle, sutured into place by episcleral sutures. The muscle operation is then completed in the usual manner. Satisfactory results were obtained in 3 patients who had secondary divergent strabismus. One case was improved by freeing Tenon's capsule laterally so that it could be drawn toward the cornea and stitched to the sclera to cover the roughened area.

Paralysis of Muscles

S. Kahoun⁶¹ reports a case of carbon monoxide poisoning, which 2 days after inhalation of the gas developed paralysis of the muscles and inflammation of the optic nerve. The levator of each upper eyelid was affected later. Recovery took place in 12 days.

OPHTHALMIA

Gonorrheal Ophthalmia

Treatment—J. C. Geiger and R. W. Burlingame⁶² recommend routine administration of *typhoid vaccine* for the treatment of gonorrheal ophthalmia. Ten million organisms of commercial *B. typhosus* vaccine are administered intravenously into the anterior fontanel. This nonspecific protein therapy produces hyperpyrexia of from 4 to 5 degrees, which may return to normal within 6 hours. The vaccine is given every 24 hours and if the temperature does not rise above 104° F the next dose is doubled; if the temperature does rise above 104° F., the initial dosage is repeated and the subsequent dose of vaccine is similarly determined. Vaccine given for 4 days is usually sufficient, preceded by intramuscular injection of adrenalin. If increase of purulent secretion in the conjunctiva returns, 3 days after this course injections of vaccine are repeated giving the same dosage as the last injection until all evidence of conjunctivitis has disappeared, and 3 smears at 24-hour intervals are negative. The appearance of the eye 24 hours after the injection of vaccine is remarkable, the amount of pus diminishes and the swelling subsides. The usual local treatment is continued. Although neither rigors nor elevation of the temperature may occur in the newborn, the results are beneficial.

Ophthalmia Neonatorum

Prophylaxis—The use of a solution of 1 per cent *silver acetate* as a prophylactic for ophthalmia neonatorum is advocated by V. C. Rambo,⁶³ because it is safer than silver nitrate. Solutions of silver nitrate may become concentrated by evaporation so that injury to the cornea may result when instilled into the conjunctival sac but the solubility of

silver acetate is such that a solution stronger than 1 per cent cannot be made at room temperature.

E. Cecchetto⁶⁴ considers the Credé method of instillation of a solution of 1 per cent silver nitrate not only ineffective for prophylaxis but also dangerous to the corneal epithelium. He advocates wiping the margins of the eyelids with cotton dipped in *sterile salt solution* or *boiled water*. If conjunctivitis results, the eyes should be treated by irrigation with a solution of *oxycyanide of mercury*, and introduction of *atropine ointment*. *Antigonococcic vaccine* is also recommended.

OPTIC NERVE

Toxic Amblyopia

Treatment—According to W. F. Duggan,⁶⁵ cases of tobacco amblyopia, without optic atrophy, respond to intramuscular injections of *acetylcholine* about as well as to intravenous injections of *sodium nitrite*. However, the effect of sodium nitrite is more prolonged and improvement in vision is more rapid.

Optic Nerve, Atrophy— Leber's Disease

Four cases of Leber's disease in 1 family are reported by J. E. Raaf and H. L. Bair.⁶⁶ In 2 of the older patients the bitemporal character of the field defect and in 1 patient in whom the disease was acute, the homonymous position of the scotomas were suggestive of a lesion in the optic chiasm rather than in the optic nerve. Roentgenologic examination of the sella was negative and evidence of pituitary dysfunction in these cases was absent.

Syphilitic Optic Nerve Atrophy

Fever Therapy—In a discussion of *fever therapy* in ophthalmology, L

Hambresin⁶⁷ points out that fever therapy produced by malaria or sulfur in oil is the only treatment of value in syphilitic optic atrophy. Fever therapy is also effective in keratitis, uveitis, and postoperative infections.

Neuromyelitis Optica

Two cases of neuromyelitis optica associated with marked loss of vision which resulted in complete recovery of vision but in incomplete recovery from the myelitis are reported by S. H. McKee and F. L. McNaughton.⁶⁸ In the first case, a male, 34 years of age, with a history of coryza developed rapidly progressing, bilateral blindness, limitation of upward gaze and lateral nystagmus. The fundus was normal and the spinal fluid presented some evidence of an inflammatory process. A diagnosis of neuromyelitis optica was made which was later confirmed. In the second case, a male, 41 years of age, presented visual disturbances, first in 1 eye and then in the other, accompanied by diminished sensitivity of the cornea in 1 eye. After the symptoms of myelitis had appeared changes were found in the fundus but the spinal fluid was negative. Incomplete recovery resulted. The following treatment was administered: in the first case, a *high caloric, high vitamin diet*, an *alkaline tonic* and 60 grains (4 Gm.) of *potassium iodide* daily; in the second case, a high vitamin diet, and daily doses of *calcium gluconate* injected intravenously during the acute stage.

Papilledema—Intracranial Disease

E. W. Newman⁶⁹ discusses the value of ocular manifestations of intracranial disease. He studied 42 cases of intracranial disease in children and juveniles and found that papilledema occurred in 95.2 per cent, loss of vision in 23.8

per cent and nystagmus in 21.4 per cent of the cases. Newman stresses the importance of these findings which suggest intracranial disease

ORBIT

Artificial Trochlea

W. Wegner⁷⁰ restored a trochlea which was destroyed by a blow sustained while skiing. An incision in the skin was made and the displaced muscle was attached to the orbit by means of an artificial trochlea constructed from a loop of a nonabsorbable suture material called synthophil. Function was satisfactorily restored.

Retrobulbar Tumor

Diagnosis —Manuel Oribe⁷¹ advocates injection of air retrobulbally to assist in the differential diagnosis by x-ray between encapsulated and infiltrating tumors of the orbit. The procedure is as follows. By means of a 10 cm needle introduced along the outer margin of the orbit, from 15 to 30 cc of air are injected to produce exophthalmos. Puncture of the conjunctival sac or of the tumor must be avoided. The exophthalmos usually disappears within 48 hours.

PERIMETRY

Colored Test Objects

The use of colored test objects in clinical perimetry is condemned by A. Magitot and A. Dubois-Poulsen.⁷² They state that in all cases in which a scotoma for color is present a corresponding scotoma for white can be found by using test objects of suitable size. The use of a 1 to 1.5 mm test object for the zone between 10 and 30 degrees and a 3 mm. test object for the zone between 30 and 90 degrees is recommended.

REFRACTION—CYCLOPLEGIA

I. S. Tassman⁷³ recommends the use of *atropine-paredrine* or *homatropin-paredrine* solution for cycloplegia. His method is as follows: about 4 minutes after instillation of 1 drop of a solution of 1 per cent atropine sulfate, in patients under 16 years of age, or 1 drop of a solution of 4 per cent homatropine hydrobromide in older patients; 1 drop of a solution of 1 per cent paredrine hydrobromide is instilled into the conjunctival sac. In some cases a second drop of paredrine is instilled. The maximum cycloplegic effect is produced in 60 minutes. No increase in the intraocular tension, irritation of the eye or of the nasal mucous membrane was observed. Rapid recovery from the effects of homatropin-paredrine cycloplegia usually occurs so that the eyes can be used normally in 8 hours. After atropine-paredrine cycloplegia the eyes may be used in about 3 days.

RETINA

Detachment of Retina

Prevention — According to A. E. MacDonald⁷⁴ excessive lifting strain is an important factor in the etiology of idiopathic detachment of the retina. Lifting of weights results in increase in the intracranial pressure which may be transmitted along the subdural and subarachnoid spaces to obstruct the central retinal veins. Excess fluid may thus collect in the retina and in the intraretinal spaces, producing detachment.

Treatment—According to H. M. Langdon,⁷⁵ satisfactory results were obtained in 4 out of 5 cases of detachment of the retina by treatment with *Shahan's thermophore*. The application of the thermophore is preceded by exposing the sclera corresponding to the area of the detachment, puncturing it with a von

Graefe knife in 1 or more places to evacuate the subretinal fluid and making multiple 1-minute applications of the thermophore with a 2 mm. tip at a temperature of 165 degrees. Both eyes are bandaged, the patient is kept quiet for at least a week, and in bed a week longer. *Stenopeic spectacles* are worn for at least 6 weeks after operation.

Diabetic Retinitis

The kidney function in 20 cases of diabetic retinitis was investigated by S. Hanum and K. Brochner-Mortensen.⁷⁶ Only 1 case revealed impairment of the kidney function. Blood tests for creatinin, urea and uric acid were normal in 19 cases.

E. Heinsius⁷⁷ encountered typical eyeground changes in 45 of 221 cases of diabetes. Changes in the retina usually occurred when the blood sugar concentration was between 150 and 350 mg. per cc. About 50 per cent of the patients with diabetic retinitis had normal or subnormal blood pressure. Hypertension in diabetic patients did not necessarily produce retinitis.

Retinitis in Pregnancy

Prognosis—J. F. Schultz and C. S. O'Brien⁷⁸ discuss the diagnosis, prognosis and management of retinitis in pregnancy. They report 47 cases which were associated with hypertensive toxemia in 2365 cases of pregnancy. Hypertensive toxemia of pregnancy is characterized by elevation of blood pressure and albuminuria and by angiospasm and angiosclerosis of the retinal vessels accompanied by edema and retinitis. About one-third of the patients who were toxic complained of visual disturbances and the extent of the changes in the retina seemed to parallel the degree of hypertension with its associated toxemia. Patients who presented normal fundi or

only angiospasm presented no evidence of permanent damage to the kidneys post-partum. Patients with angiosclerosis or retinitis presented evidence of permanent damage when examined 4 months after delivery. Schultz and O'Brien deduce that the prognosis for patients with organic changes in the vessels of the retina or with retinitis is not favorable. Patients who present normal fundi or angiospasm should be treated conservatively, but if angiosclerosis or other organic changes in the vessels of the retina appear the uterus should be emptied

"Retinitis Pigmentosa Syndrome"

E B Streiff and C. Zeltner⁷⁹ report a case of Laurence-Moon-Baird-Biedl syndrome characterized by mental retardation, adiposogenital dystrophy, polydactylia and peripheral tapetoretinal degeneration of the type found in retinitis pigmentosa. Consanguinity in the parents occurred in 24 per cent of the cases

TRACHOMA

Treatment — L A Juhanelle, R. Soty, J F Smith and A C Lange⁸⁰ report the results of their experiments with *antimony potassium tartrate* on the course of trachoma. They found that tartar emetic inactivates the virus of trachoma *in vitro*. It seems that clinically tartar emetic, administered intravenously, may be beneficial in cases of long-standing trachoma presenting scarred tarsal conjunctiva in which local treatment usually produces an exacerbation, in cases which present papillary hypertrophy, in cases of severe infiltrations of the cornea and in cases of ulceration of the cornea

TRIGEMINAL NERVE NEURITIS

Treatment — Three cases of nasal nerve syndrome which were relieved by

tuberculin are reported by C. Charlin⁸¹. Two of these were relieved simply by a Mantoux test performed in the course of a routine examination. The third patient affected for a period of 12 years by essential neuralgia of the trigeminus was relieved after prolonged treatment with tuberculin. Neuritis and neuralgia of the trigeminal or other nerves may arise from tuberculosis of the ganglion. Charlin recommends performing a tuberculin test in all cases of nasal nerve syndrome before attempting any other form of treatment

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OTORHINOLARYNGOLOGY

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LARYNGOLOGY AND DISEASES OF THE NECK

By LOUIS ZOLO FISHMAN, M.D., M.S.

LARYNX

Anatomy and Physiology—*Ventricle of Morgagni*—Freedman¹ reviews the structure of the region located between the true and false cords of the larynx. In man, the laryngeal ventricle exists usually in the form of a shallow, slit-like *cul-de-sac*. Phylogenetically, it is vestigial and represents in man the remains of the ventricular air sacs of the larynx present in other vertebrates. According to Freedman, the function of ventricular sacs is that of an "oilcan of the vocal cords." He explains that the clearing effect on the voice as commonly produced by the drinking of water or swallowing of saliva is due to the effect of the attending physiologic movements of the larynx upon the sacculus. This consists of a compression of the sacculus to "squeeze out the last drop of valuable mucus to lubricate and cool off the overexcited vocal cords." His physiologic concept is intriguing, but highly improbable; actually, the high degree of development of speech in man is associated with retrogressive changes of the laryngeal air sacs.

Diagnosis—Roentgenologic Examination—A comprehensive and skillfully prepared monograph by Waldapfel² on peroral roentgenography of the larynx appears this year. Although some questions may arise regarding the merit of this "laboratory" procedure as another adjunct to the present day methods in

the diagnosis of laryngeal disease—and there are isolated instances undoubtedly in which such an examination may be of assistance—the procedure is of great academic interest to the laryngologist. The method is relatively simple: After applying a topical anesthetic to the hypopharynx, a properly encased and properly shaped film, its surface in the lateral plane, is inserted into the hypopharynx. The length of the film corresponds to the length of the larynx (from tip of epiglottis to inferior border of cricoid cartilage); its width differs, conforming to the pyramidal shape of the hypopharynx. By directing the roentgenrays from in front of the larynx against this film, a roentgenogram of the larynx is obtained. This anteroposterior study is enhanced by the elimination of the vertebral column from the negative. The interpretation of such a negative is subject necessarily to an intimate understanding of the structure of the larynx in every respect.

Pyocoele

Surgery—Freedman (*loc cit*) makes a most instructive report, probably the first, of a *pyocoele* of a ventricular appendix or sac of the larynx. Its clinical (preoperative) appearance was that of a neoplasm of the false cord and ventricle of the larynx; repeated biopsies revealed evidence only of chronic inflammatory changes. *Exploratory thyrotomy* was performed with the view in mind of do-

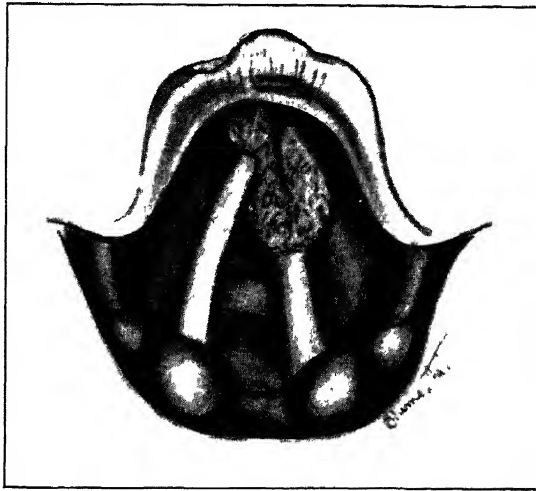


Fig 1—The larynx before operation, showing a tumor on the anterior half of the left vocal cord, ventricular band and subglottic region. It also shows fixation of the left vocal cord (Laryngoscopic picture) (Freedman Arch Otolaryngology)



Fig 2—Pyocele of a congenital air sac of the ventricle of the larynx. The drawing represents the thyroid cartilage split open for laryngofissure, showing the tumor on the left vocal cord. The air sac is diagrammatically shown in stippled lines in the right upper part of the picture (Freedman Arch Otolaryngology)

ing a *laryngectomy* if indicated. The author's description of the last stages of the procedure is potentially a classic. "When the mass was freed from its anterior and superior attachment to the thyroid cartilage there was a gush of thick yellow pus. On carefully exploring for the origin of this pus I saw a gaping, velvety, puckered mucous membrane-like opening. This finding was so unexpected and unusual that I asked my

hyoid bone upward and outward toward the external auditory meatus of that side, to end in a blind sac" Recovery was uneventful.

"Exploratory" thyrotomies as such are performed infrequently by skilled laryngologists. But thyrotomies and laryngofissures are quite commonly resorted to in certain well-defined diseases of the larynx. In this case, an "exploratory" procedure was of unquestionable

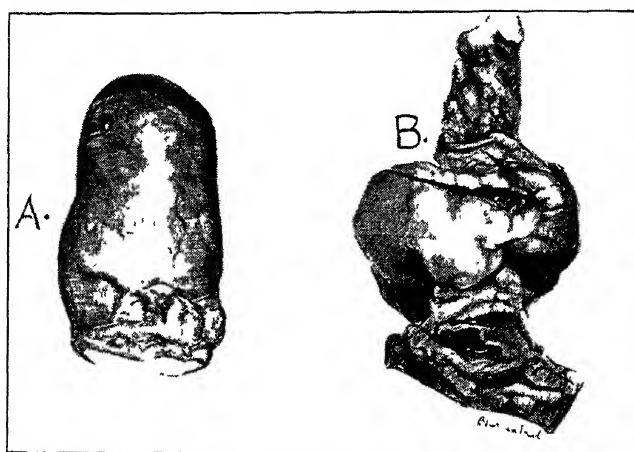


Fig. 3. *A*—Sac of a pyocoele. The lower part is the open end, which communicates with the ventricle. *B*—Tumor mass excised at operation. The black horizontal line running across the center of the photograph represents the entrance to the ventricle. The true and false cords are partly replaced by tumor. (Freedman. Arch. Otolaryngology.)

assistant what he thought I had encountered. Without any hesitation he suggested that I had cut the esophagus! My second assistant, who had a better knowledge of the more intimate structures of the neck, hinted at a severed thoracic duct, since we were working on the left side.

"I decided to explore further in order to see whether I had merely cut the channel that conveys gross food to the stomach or had been so indiscreet as to sever the finer duct, which carries the essence of digestion to the blood stream. This opening admitted the little finger comfortably. A probe passed into it traveled along under the ala of the

merit. Though the designation "exploratory" to an operation on the larynx by the external route is a dangerous one, nevertheless, there is a need for it in the practice of laryngology. Its indications should be very strict.

Stenosis

Treatment—With improvements in the treatment of laryngeal diphtheria, cases of stenosis of the larynx following this disease have become more and more infrequent. The same may be said regarding the incidence of cricoid cartilage destruction resulting from too high tracheotomies in children. On the other hand, there is a rise in the number of

traumatic deformities of the larynx, due mostly to an increase in the use of rapid forms of transportation.

The problem of repair in the latter types of laryngeal stenosis deals mostly with that of returning the cartilaginous supports of the larynx to their former position, thereby widening the glottis. Looper³ suggests a novel plastic operation in these cases, consisting of the isolation of the left half of the hyoid bone, which is then swung down and fixed anteriorly between the 2 thyroid plates, previously cut through. The right half of the hyoid bone is left intact to avert sequestration of the whole. Care must be taken in freeing the hyoid to leave some tissue affixed to its upper, lower and anterior surfaces as a measure of attaining better blood supply and protection; also, perforation of the pharynx or larynx is to be avoided.

Paralysis

Motor dysfunctions of the larynx have been discussed here each year. The question as to whether or not Semon's "law" is of value in these cases, not only to explain the pathogenesis, but especially as a means to indicate treatment and render a prognosis, is still a focal point of controversy. It is strange that even laryngologists hold fast to this idea of Semon's that has long past proved its inadequacy. For the present at least, the clinical evaluation of laryngeal paralysis can only be determined, so far as possible, on the basis of undisputed anatomic and neurophysiologic data.

The following excerpts from the Bulletin of Green's Eye Hosp.⁴ are significant and reflect the adherence to rigid principles of scientific dogma.

"It seems desirable to discontinue the use of the term 'abductor paralysis,' which implies a lesion of only those

fibers to the posterior cricoarytenoid, unless it can be proven that such isolated paralysis is actually present and that the case is not one of complete paralysis of the recurrent nerve. The laryngeal image in such cases is of little help in differentiation and indeed there are few cases in which one may by inspection of the affected cord determine definitely the type and situation of the lesion, the usual text book descriptions to the contrary notwithstanding . . . This relationship of the 9 laryngeal muscles, 4 nerves and bilateral cortical and medullary centers, all delicately coordinated in performing the complicated motions of the vocal cords, prohibits an easy study of isolated motions of these. Paralysis of isolated laryngeal muscles probably is of infrequent occurrence and clinical experience indicates that there is remarkably little variety in the laryngeal image in cases of paralysis involving the larynx. Even competent laryngologists are not always agreed on the appearance of a cadaveric cord. It is probable that many cords described as cadaveric or intermediate in position may in reality lie nearer the midline than in the intermediate situation . . . Paralysis of central origin may affect any group of nerve or muscle fibers and in these, in spite of the stronger impulses for adduction, it seems unlikely that fibers for abduction should be affected first invariably.

"An infranuclear lesion of a nerve is usually complete and even if the fibers to the abductor muscles were invariably more delicate, one would expect the abductor fibers to be affected first occasionally. Granting the similarity between abductors of the larynx and extensors of the extremities in their susceptibility to certain specific agents, it is still unreasonable that the abductors should be first involved when the paralysis results from

causes affecting flexors (adductors) and extensors (abductors) equally.

"It is probable that a small nerve like the recurrent will, when paralyzed by peripheral causes, usually be affected in all its branches which are distal to the lesion except perhaps in the occasional

Traumatic Neurogenic Paralysis

Bilateral Recurrent Laryngeal Paralysis—"Post thyroidectomy *bilat-eral* abductor paralysis," or destruction of both recurrent laryngeal nerves, represents a type of laryngeal paralysis that is so constant in its clinical course that

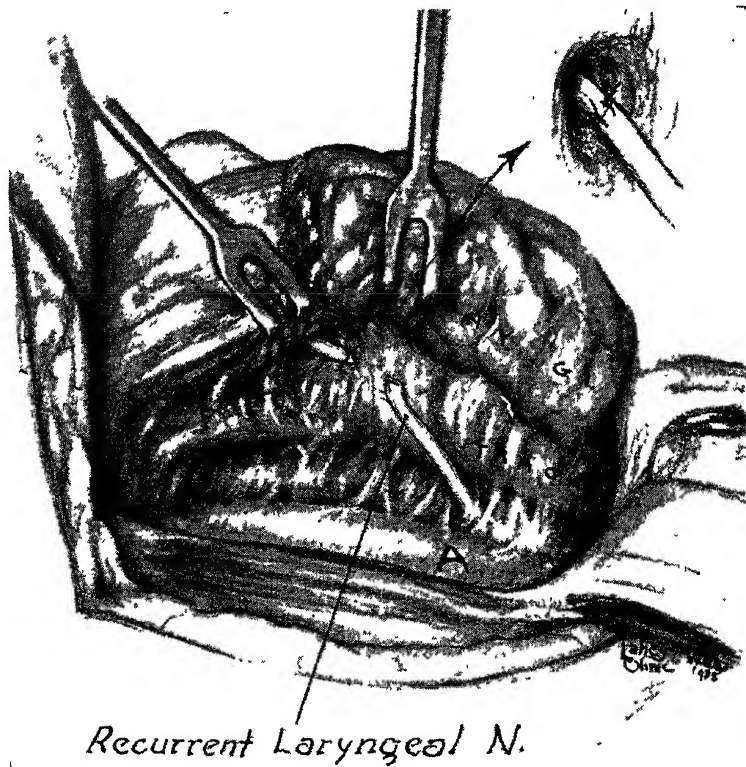


Fig. 4—This figure was drawn at the operating table to demonstrate the location and suture of the recurrent laryngeal nerves in 2 cases. The nerve had been severed just below the point where it entered the larynx. Note the black silk ties found on each end of the severed nerve. The inset illustrates the fine black silk vessel sutures inserted on either side of the approximated nerve to oppose fibers conveying similar impulses (Lahey and Hoover: *Annals of Surgery*, Oct., 1938)

case in which the agent is one such as lead or ether, when its action may conceivably be selective on nerve or muscle.

"Although the recurrences are said to be similar in their vulnerability to that of the optic, auditory and splanchnic nerves and of the spinal cord, yet, even if this be true, it seems doubtful that this vulnerability is as important in relation to paralysis as is the anatomic course of the nerves in the neck."

laryngologists recognize the condition almost as an entity.

Prophylaxis—Lahey calls the thyroid surgeon's attention to a long-known fact, that the practice of observing the patient's voice during the final stages of thyroidectomies is not essential, but rather misleading and even dangerous. Obviously, when the patient becomes hoarse, the recurrent nerve has been destroyed, and, often, too late for the

patient. What is worse, 1 nerve may be cut without any apparent change in voice immediately. Lahey exhorts the surgeon to rationalize this phase of thyroidectomies by finding these nerves, even to the extent of isolating them, so as to keep them away from the line of dissection and hemostasis. Such a departure from former technic has reduced the incidence of this type of accident in the Lahey clinic from 1.6 per cent to 0.3 per cent (latter incidence in 3000 recurrent laryngeal nerve exposures).

Treatment—The treatment by nerve anastomosis has been reported adversely by W. Stevenson. This year, Lahey advocates either an *end-to-end anastomosis* of the severed ends of the recurrent nerve, or, if a deficiency of more than $\frac{1}{2}$ inch is found, of following Colledge and Ballance's procedure of anastomosing the distal end of the recurrent with the proximal end of the phrenic nerve. The phrenic nerve carries respiratory impulses, coinciding somewhat with the neurophysiologic characteristics of the recurrent. For this reason, this nerve should be more adaptable than the descending branch of the hypoglossal to such an anastomosis, as employed earlier by Frazier. Lahey suggests that any attempts at anastomosis should be made not later than 3 months following the onset of such a paralysis. He recommends it as a feasible surgical procedure (see report of last year to the contrary), and states that an anatomical difficulty is evident in the inability to place abductor and adductor fibers of this dual nerve in their proper relationship.

In recommending the above, Lahey qualifies it by reporting 3 cases in which the nerves were found isolated and successfully sutured, without any return of function 3 and 6 months following anastomoses (time of publication). One important prerequisite for such work not

mentioned is the necessity of obtaining a condition of immobilization of the larynx against its wide excursions within the neck, during swallowing particularly. It is noteworthy that in the face of such movements anastomoses of the recurrent nerves may be disrupted readily.

Tuberculosis

Treatment—Since there is a unanimity of opinion that tuberculosis of the larynx is secondary to that of the lungs, all therapeutic concepts regarding this complication have their emphasis directed on an adequate program against the pulmonary infection. The rationale of such a plan is so obvious to the physician that, too often, there is created in him by virtue of it a decidedly deleterious psychologic attitude of phlegmatism toward diseased units elsewhere in the tuberculous patient. Whether it be this sense of exaggerated therapeutic rationalism or a sense of therapeutic nihilism motivating these so-called conservatives, there must be a discrimination made between the abstemious and the genuinely conservative. The latter title is an unfortunate one when set up as a standard of measure in the practice of medicine, successful therapy as implied can be neither radical nor conservative, but, rather, adequate.

In some measure, Dworetzky's⁶ report tends to encourage the focusing of therapy on the pulmonary lesion to the exclusion, to a certain degree, of laryngeal complications. On the basis of his classification, tuberculous infection of the larynx occurs more frequently by surface inoculation than through the blood stream; infection by way of the lymphatics occurs, but is difficult to prove.

Carcinoma

Treatment—*Extensive resections* of carcinomas of the larynx and hypo-

pharynx (laryngopharyngectomy) is advocated by Orton.⁷ He reports a number of cases of carcinoma involving these regions, better known as extrinsic carcinoma of the larynx. These tumors are usually of the squamous cell type. Metastases to the cervical lymph nodes are the rule and occur early. Orton refers to Trotter's operation and ideas, as follows:

"Features of operation—(1) The isolation of the area of gland dissection from the visceral planes of the neck by suturing the sternocleidomastoid muscle to the prevertebral muscles; (2) the removal of the thyroid cartilage and the cornu of the hyoid bone before the pharynx is opened, so that the growth may be palpated through the pharyngeal aponeurosis, (3) the closure of the wall of the pharynx in early stages, by which immediate reunion of it may be obtained, (4) the combination of the operation with a plastic procedure when necessary," and in conclusion, "the future development of the subject probably lies then, on the one hand, in the exploitation of radium, and on the other in that of early diagnosis. Should the latter be cultivated on an adequate scale, the operative excision of small pharyngeal epitheliomas will probably long remain a legitimate field for the surgical adept and a field in which he may look with confidence for cures with little risk to life and no persistent disability."

Brunner⁸ describes a case of melanoma of the pharynx in his classical style. A primary melanoma, the size of a walnut, was removed from the posterior wall of the pharynx by lateral pharyngotomy (Trotter's operation). Exitus resulted from a second growth rather than from the first, occurring 3 years after the operative procedures. The second tumor was also a melanoma, involving the petiolus of the epiglottis

but which failed to respond to all therapy. Of interest is the fact that there was no recurrence of the first tumor, as proven by post mortem. Brunner discusses the pathogenesis of the second growth, inclining to the belief that it represented a separate neoplastic process and not one due to contact or implantation. The first (of hypopharynx) produced cervical metastases relatively late, whereas the second (of larynx) did so relatively early.

Radiosensitivity—The use of histologic grading of tumors as a guide to irradiation therapy, unfortunately, is not proving its merit as time goes on. Harris and Klemperer studied a series of 32 cases of carcinoma of the larynx microscopically (extrinsic and intrinsic, but excluding those of the hypopharynx); all were treated by the so-called method of Coutard alone. Their conclusions are, "Grade of cellular differentiations, mitotic count, anaplasia of the cells, reaction in the stroma and location of the neoplasms were considered, but no clear-cut criteria could be established—that for protracted roentgen therapy the histologic structure is of minor importance in determining the radioresistance of laryngeal carcinomas."

These findings are in keeping with the experience of Quick.¹⁰ After giving a fine historical review of the surgical and radiation methods of treatment for these tumors, 12 cases, the greatest number of which were extrinsic carcinomas of the larynx, are reported, in which uniformly good results followed treatment by radium, radon seeds and/or by roentgen rays. Cures of long duration were obtained despite differences of the tumors in location and structure. This evidence—no mention is made regarding the incidence of cervical metastases—warrants serious thought by surgeons, even though Quick cites a few cases in which

the physiologic end result of irradiation was equivalent to that obtained by laryngectomy. An evaluation of this rather astounding report in the light of certain experiences to the contrary is difficult; for the present, too many facts are irreconcilable with each other.

Just as controversial is Orton's¹¹ report based on his experience with 102 operated cases of laryngeal carcinoma. The problems of classification and indications for operation have been reviewed before. Orton's procedures and results are contrary to the concepts of many well-known clinics. For example, a case is cited of anaplastic carcinoma of the pyriform sinus removed surgically; this patient is living, 6 years following the operation. Orton has performed laryngectomies also in the face of infiltrative lesions, as evidenced clinically by vocal cord fixation or by metastatic cervical lymphadenopathy. There can be no doubt regarding the type of pathology and surgical results obtained in these cases as made obvious to the reader when he sees the startling photographs of these laryngectomy specimens of Orton. Unfortunately, no detailed case histories are given. But the results are revealing: In 94 cases of laryngectomy, including 1 case of lateral transhyoid pharyngotomy, 57 are alive and well; 9 are dead from other causes; 5 died within 3 weeks of operation, 23 are dead from recurrences.

Delayed Irradiation Effects—Inasmuch as prolonged irradiation therapy of goiters is known to have a destructive effect on the adjacent larynx, it is well to consider in this chapter similar destructive sequelae, by the same procedures, involving the trachea. Clerf and Putney¹² summarize the pathology of immediate and delayed reactions to prolonged irradiation of the neck. Irradiation of a malignant neoplasm of the

larynx is not without its danger to the normal anatomical laryngeal structure. But, this eventuality is of no significance when one considers the character of the disease to be treated. These writers refer to the disproportion between the mode of therapy and the disease in the use of the roentgen ray as an elective measure in exophthalmic goiter. In the case reported, the trachea was stenosed and further occluded by a granulomatous mass. A preliminary tracheotomy was performed and the mass removed surgically; atrophic changes were permanent. Usually, these cases evidence destructive effects within the larynx. But, in the above instance, the reverse conditions were found, namely, the larynx was normal, but the trachea just below it was as described.

New Instruments—A laryngeal carrier for radon seeds has been constructed for Simpson,¹³ utilizing a Jackson bronchoscope for its application. By this means, radon seeds may be placed perorally near or to the surface of an intralaryngeal growth. The radon seeds are kept in position in the larynx for from 6 to 10 minutes, or for a longer time if advisable. Treatments are repeated until approximately 500 to 750 millicurie hours have been given. Intralaryngeal treatment is reinforced by treatment with the radium bomb from the external surface over the larynx.

Cinematography—The following illustrations by Pressman and Hinman¹⁴ should be helpful in standardizing the equipment and establishing a routine for this work. As evident from the enlargements, the clarity which can be obtained of the photographed laryngeal image should place such studies on a high plane for research and teaching.

In brief, the factors involved in this set-up are:

Source of light—Jackson laryngoscope.

Bulb—4 watts; 6 watts, preferable. Special arrangement—2 bulbs

Camera—De Vry 16 mm motion

Extension tube—advance of lens $\frac{1}{4}$ inch.

Lens—2 inch, f. 15.

Distance (lens to vocal cords)— $11\frac{1}{2}$ inches

Depth of focus—11 to $12\frac{1}{2}$ inches

Complementary Distance (tube between lens and mouth of laryngoscope). Cardboard— $4\frac{1}{4}$ inches long Properly notched to fit

NECK

Congenital Abnormalities

Branchial Cysts—The term “lateral” designates cysts of the neck and branchial derivation in contradistinction to the thyroglossal varieties which are in the median line of the neck.

Among a number of writers this year, Hicken and Popma¹⁵ report a few cases;

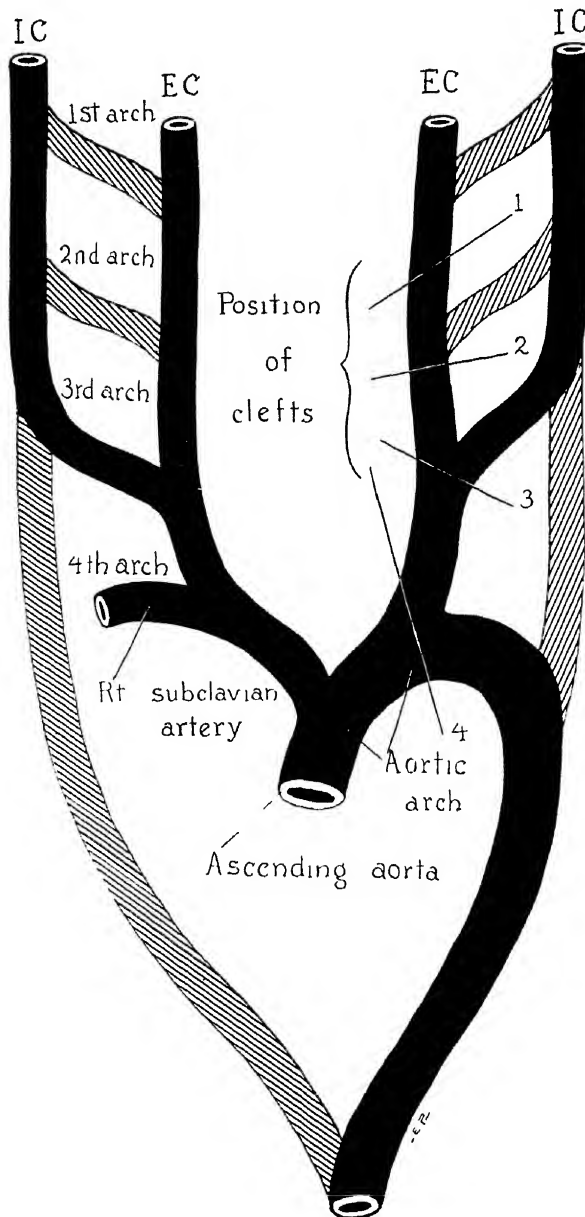


Fig 5—Schematic drawing of the human aortic arches, and their transformation into the mature arterial system. The shaded vessels disappear and the black vessels persist. EC, external carotid artery, IC, internal carotid artery. (Courtesy, American Journal of Surgery, Feb 1938)

Jackson¹⁶ reports 13; Ladd and Gross,¹⁷ 82. Included in the latter are a number of cases of cysts of the auricle and cartilaginous rests of the neck. Jackson is inclined to support Wenglowski's (1912) conception that lateral cysts of the neck arise from a persistent thymic "duct," anlage of the thymus gland. Ladd and

between the bifurcation and end at the inferior part of the posterior faucial pillar, representing the extent of the second branchial cleft.

In order that a derivation from the third cleft be considered, the course would have to be posteroinferiorly to the glossopharyngeal nerve which runs in

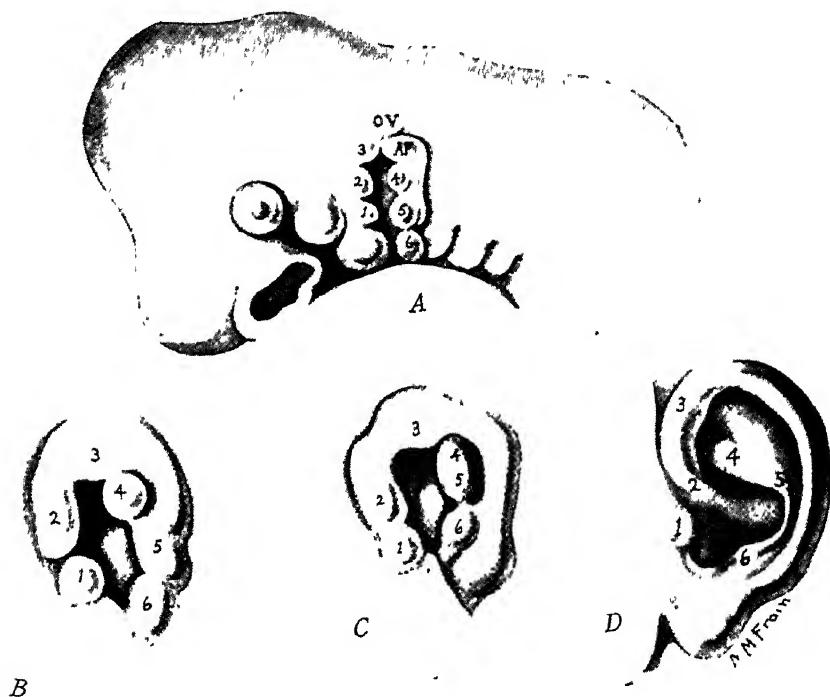


Fig. 6—Stages in development of the external ear, adapted from His and from Arey's "Developmental Anatomy." A, 11 mm B, 13.6 mm C, 15 mm D, adult 1, 2, 3, elevations on the first branchial arch 4, 5, 6 elevations on the second arch af, auricular fold, ov, otic vesicle, 1 tragus, 2, 3, helix, 4, 5 antihelix 6 antitragus Small congenital fistulae opening on the ear or just in front of the tragus probably represent a failure of fusion of 2 adjoining elevations (Courtesy, American Journal of Surgery Feb 1938)

Gross also review the development of these cysts, but believe that they are derivatives from the branchial apparatus.

A derivation of lateral cysts of neck from the second branchial cleft and pharyngeal pouch is supported by the constancy with which these cysts are located in relation to the sternocleidomastoid muscle, bifurcation of the common carotid artery and tonsillar fossa, namely, they are anterior to the muscle, course

this arch. Such a course has as yet not been demonstrated.

Cartilaginous rests or *tags* of the neck are rarely seen. They contain small bits of cartilage, reaching for short distances into the superficial tissues and are solid, without a lumen or fistulous opening. Cysts are lined by stratified squamous or columnar (ciliated or nonciliated) epithelium. The presence of lymphoid tissue in the walls is accounted for on the



Fig 7—Branchial fistula in a 2-year-old girl. Sinus noted since birth. Intermittent discharge of clear mucoid fluid. The small cutaneous orifice lies just inside of the medial border of the sternocleidomastoid muscle. Sinus extended to the tonsillar fossa. (Courtesy, American Journal of Surgery, Feb. 1938.)

Fig 8—Small sinus in a 7-year-old girl, noted since birth. At operation the tract was found to be only 2 cm. in length. (Courtesy, American Journal of Surgery, Feb. 1938.)

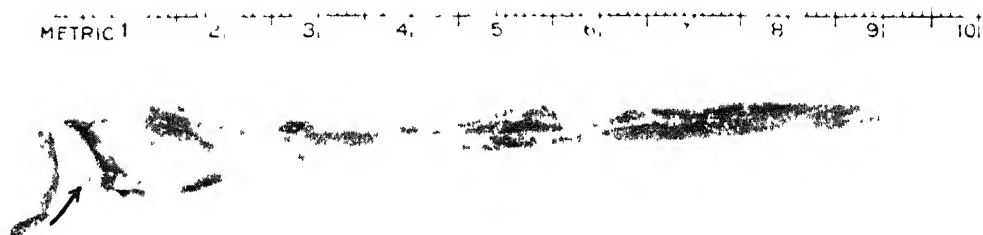


Fig 9—Specimen of branchial sinus as removed at operation. The tract extended from the skin just above the suprasternal notch to the base of the tonsil. Arrow points to the small cutaneous orifice. When opened, the tract was found to be lined with a squamous epithelium. (Courtesy, American Journal of Surgery, Feb. 1938.)



Fig 10—Roentgenogram following lipiodol injection of branchial sinus. The irregular extravasation along the lower portion of the tract indicates cavitation from secondary infection and suppuration. (Courtesy, American Journal of Surgery, Feb. 1938.)

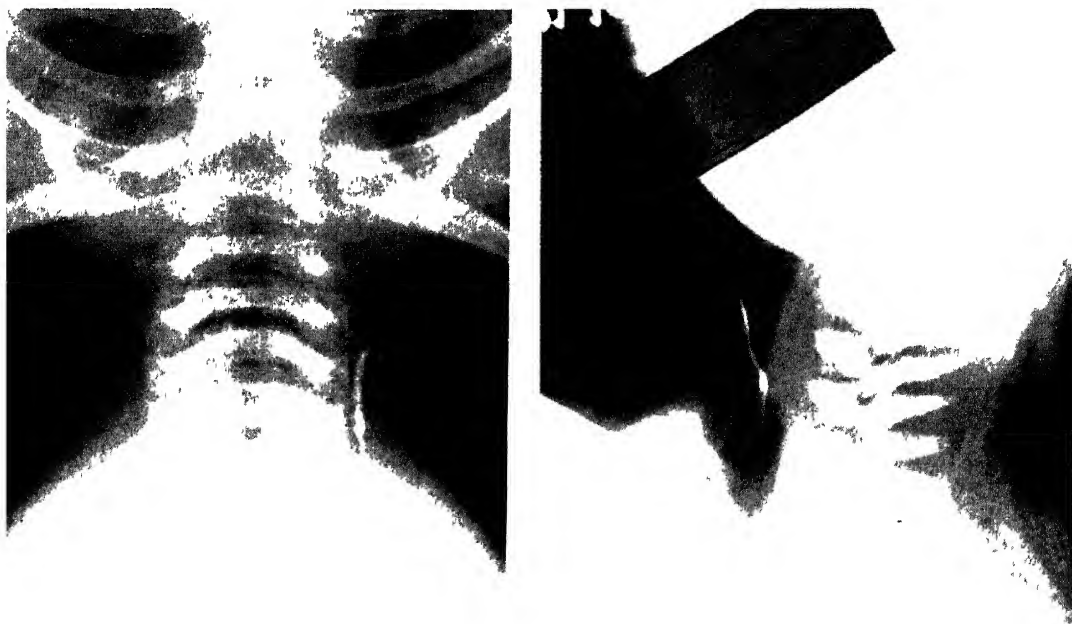


Fig 11—Injection of a branchial fistula with an aqueous suspension of barium. Subsequent operation showed that this visualized portion of the tract represented only half of the sinus which extended upward to the posterior tonsillar pillar. (Courtesy, American Journal of Surgery, Feb. 1938.)



Fig 12—Right branchial cyst in a 1-year-old girl. In the anterior view of the neck there is a small cutaneous orifice which occasionally discharged mucoid fluid. The cyst was present at birth. (Courtesy, American Journal of Surgery, Feb. 1938.)

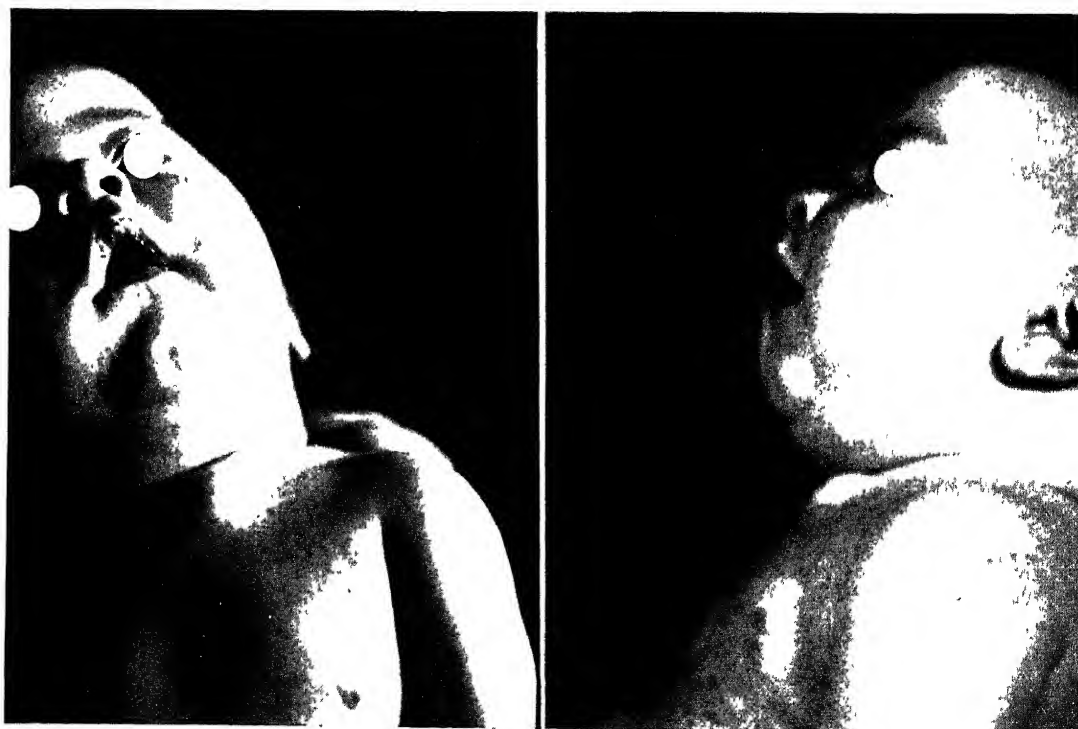


Fig 13—Left lateral cervical cysts in a 4-month-old baby. At operation a sinus was found leading from the cyst up to the base of the tonsil. (Courtesy, American Journal of Surgery, Feb. 1938.)

basis of chronic infection rather than being significant of a thymic genesis.

Treatment is complete surgical dissection of the cyst and its fistulous tract. The injection of sclerosing agents into the cysts merits little consideration. Solid tabs are excised relatively easy.

dent power of irregular growth and penetration. By some means, the primitive jugular sac or portions of it fail to establish a communication with the venous system, but may retain the power of growth inherent in the process of endothelial sprouting and penetration



Fig 14—Left branchial cyst with secondary infection and abscess formation (The mass was tender and the overlying skin was reddened) Incision and drainage performed before excision was possible (Courtesy, American Journal of Surgery, Feb 1938)

Cystic Hygroma

In an extensive and commendable work of investigation, Goetsch¹⁵ reports his results based on 12 cases of hygroma. Ten occurred in the neck and 2 in the axilla. A historical survey of the subject is presented in detail. The present-day concept regarding the origin of these tumors is that they are derived from lymphatic rests which, in the case of the neck, are remnants of the primitive jugular sacs and which possess an indepen-

characteristic of the development of the normal lymphatic system. Canalization of these sprouts results in cyst formation.

Although hygromas are benign pathologically, they may be clinically malignant by virtue of their extensive invasion, displacement and compression of the tissues represented in the environment of the new growth. As a consequence, too, symptoms are diverse and are in proportion to the size and location of such tumors.

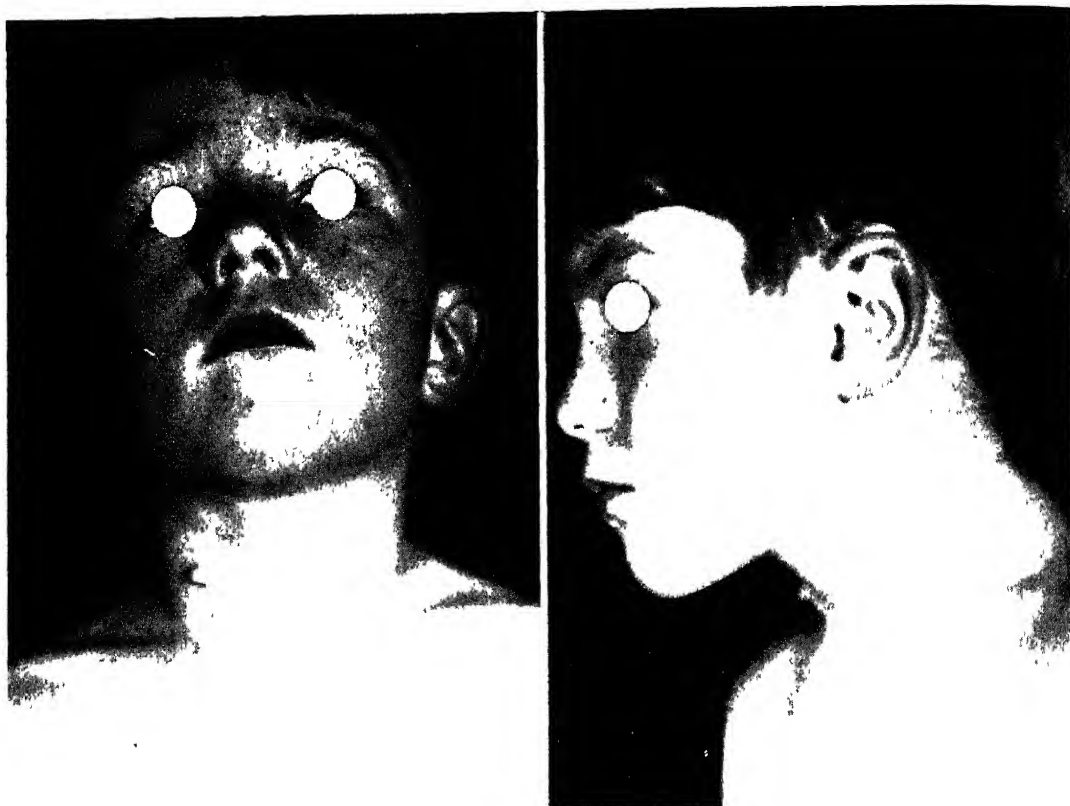


Fig 15—Pedunculated cutaneous tab containing cartilage (Courtesy, American Journal of Surgery, Feb 1938)



Fig 16—Bilateral pedunculated tabs on the neck of an infant. Each lesion contained a rod of cartilage extending upward for 1 cm along the medial border of the sternocleidomastoid muscle (Courtesy, American Journal of Surgery, Feb 1938)

A dreaded complication is that of secondary infection of hygromas, either from systemic or from more local sources. Because of the multilocular arrangement of the cysts, treatment of a hygroma abscess by surgical drainage is prolonged if not futile and even fatal.

Errors in diagnosis before operation are frequent and at times a correct diagnosis is well-nigh impossible.

The following presumptive diagnoses were made before hospitalization in the

Clinical Course and Prognosis—

Untreated, these masses enlarge, sometimes slowly, sometimes rapidly. Death in children results from malnutrition. Hygroma is seldom met with after puberty, since previous infection results either in death or in a spontaneous cure. Infection and sepsis following simple incision for drainage is often fatal.

In Goetsch's series, there was no instance of spontaneous rupture or even threatened rupture of a hygroma, even

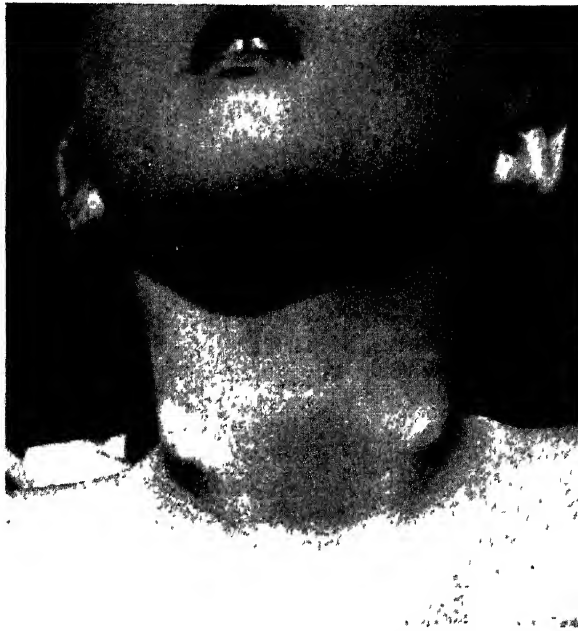


Fig. 17—Bilateral sessile tabs of the neck, each of which contained an irregular piece of cartilage about 1 cm. in length (Courtesy, American Journal of Surgery, Feb. 1938)

series reported by Goetsch: hematoma, angioma, tuberculous adenitis, simple cyst, lipoma, branchial cyst, goiter and benign lymphatic tumor. Lymphoblastoma and Hodgkin's disease were considered in a case of hygroma secondarily infected.

In differentiating branchial cysts, it should be remembered that these are usually single, unilocular and smaller than hygroma; there is no associated atrophy of the overlying fat and skin in the former.

in several cases in which the skin overlying the tumor had become so thin as to be almost transparent.

Treatment—Early and radical *surgical resection* is treatment of choice. Palliative treatment is highly dangerous because of danger of an intercurrent tonsillitis or bronchitis producing a secondary infection of hygroma and because of possible growth, particularly into such areas as mediastinum.

The author discusses the various types of therapy which have been recom-

mended by some. *Radium* is a favored treatment of Figi (Mayo Clinic), but is refuted as such by Goetsch. The latter does recommend it and *roentgen-ray* therapy, however, in cases of poor surgical risk or of extensive involvement.

tion, or at any rate as long as possible in order to facilitate the procedure and thus assure complete extirpation. In no instance was a communication with the vein found even after careful search and probing.



Fig. 18—Scheme of operative incisions for removal of a branchial cyst or fistula. In the lower incision, an elliptical piece of skin includes the cutaneous orifice of the sinus. If the tract is long, and extends up to the pharynx, a second incision is made superior and posterior to the first. The sinus tract can then be brought out through this higher wound and the dissection can be carried above this level. The disfigurement from these horizontal wounds is minimal and hence the "stair steps exposure" is superior to an incision which runs parallel to the sternocleidomastoid muscle. The shaded area represents extent of subplatysmal dissection between the 2 wounds. The fistulous tract courses medial to the sternocleidomastoid muscle, S, lateral to the external carotid artery, EC, anterior and medial to the internal carotid artery, IC, and beneath the posterior belly of the digastric muscle PD. (Courtesy, American Journal of Surgery, Feb. 1938.)

Dissection at times is difficult because of the peripheral fibrosis and the adhesions by which the tumor is attached to vascular sheaths in the neck and particularly to the jugular vein. The vagus nerve, carotid artery and jugular vein may be incorporated within the tumor. In dissecting a hygroma, it is important to preserve it intact throughout the opera-

Deep Infections

Treatment — Laterally, successful treatment implies that the proper principles of therapy were followed. But, success in the treatment of deep infections of the neck is not a foregone conclusion resulting from adherence to well-established medical and surgical principles. The word "principles" as ap-

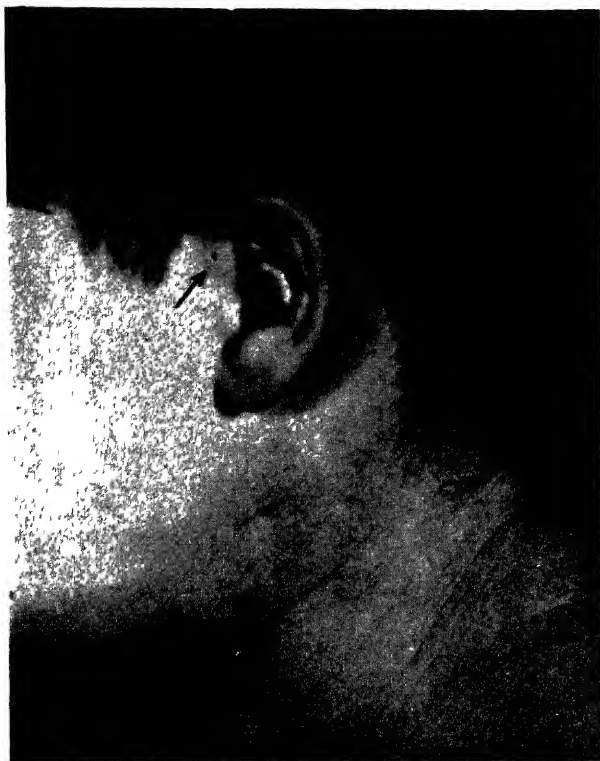


Fig 19—Small sinus which opens on the anterior portion of the helix. The sinus led downward and forward for a distance of 1 cm. (Courtesy, American Journal of Surgery, Feb. 1938.)



Fig 20—Recurring inflammatory lesion anterior to the ear which began in a small sinus just in front of the tragus. (Courtesy, American Journal of Surgery, Feb. 1938.)

plied here, particularly, becomes all too dignified and pretentious.

Many publications appear from time to time describing the anatomy of the neck and its adjoining structures, the head and thorax; the innumerable etiologic factors that are concerned in such infections are to be found in profuse

palliative type of therapy serves the physician well in the practice of his "art."

Keefer¹⁹ reports a case of *suppurative mediastinitis* in a man, 46 years of age, following acute tonsillopharyngitis. Although there was no palpable mass in the neck, the pharynx was edematous and roentgenologic examination revealed



Fig. 21—Congenital fistula of aural lobule. The sinus was less than 1 cm. in length. There was intermittent discharge of a mucoid droplet from the small orifice. (Courtesy, American Journal of Surgery, Feb. 1938.)

descriptions captioned by a multitude of titles. Since a variety of tissues and organs are readily accessible to these infections, it is not surprising that almost innumerable pathologic eventualities exist in the course of any one case of deep neck infection. The same broad statement may be made regarding symptomatology, complications and prognosis. For these reasons, articles have been selected to emphasize the successful results of coincidental treatment, as well as premeditated. It can be said that the former

the presence of an abscess in the posterior mediastinum. This was drained by resecting a portion of the second, third and fourth ribs close to their articulation with the spine; 300 cc. of thin purulent material was obtained. Drainage and supportive measures, including 2 blood transfusions, assisted in the patient's recovery. A similar case in a boy, 1 year of age, following a "cold" and subsequent retropharyngeal abscess is reported by Jones, Brown and Fine.²⁰ It seems that in this case, it was necessary to turn

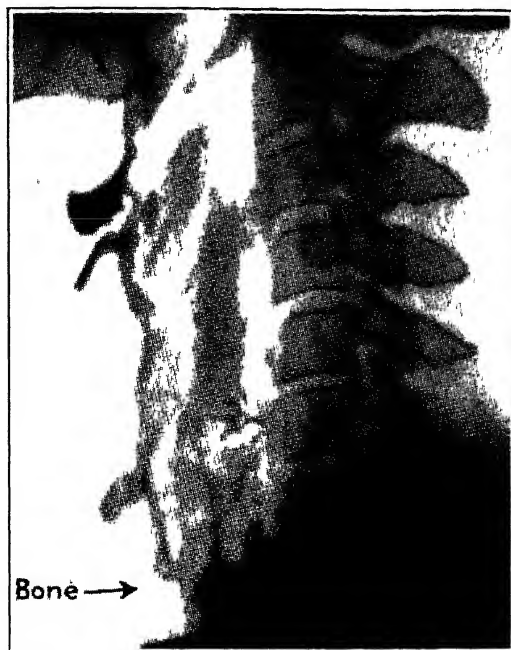


Fig 22—Emphysema of the neck and a bone, indicated by arrow, in the esophagus (Courtesy, J A M A, Sept 10, 1938)



Fig 24—Mediastinal abscess rupturing into the bronchus, injection of iodized poppyseed oil (Courtesy, J A M A, Sept 10, 1938)



Fig 23—Barium sulfate passing into the posterior mediastinum and rupturing into the bronchus (Courtesy, J A M A, Sept 10, 1938)

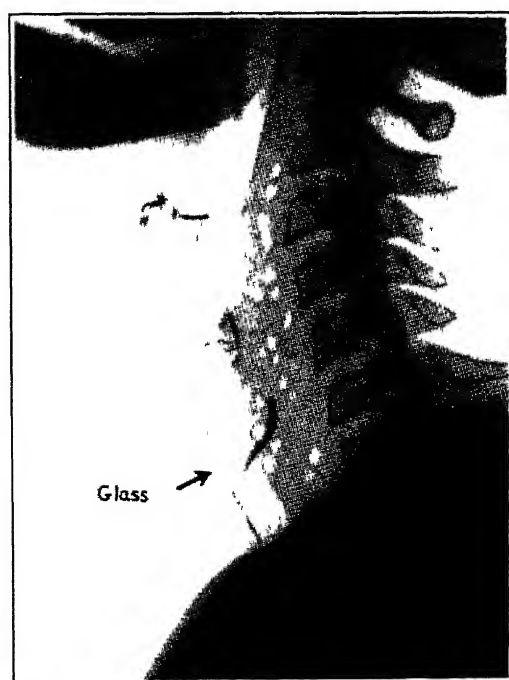


Fig 25—A piece of glass, indicated by arrow, perforating the esophagus and emphysema in the prevertebral space (Courtesy, J A M A, Sept 10, 1938)

TABLE I
110 CASES OF SUPPURATIVE MEDIASTITIS

Etiologic Factor	No of Cases	Per Cent	Operative Result		Nonoperative Result	
			Recovery	Death	Recovery	Death
Perforation cervical esophagus.	64	58.1	24	9	4	27
Suppurative cervical lymphadenitis	13	11.8	7	6		
Retropharyngeal abscess	11	10.0	6	3	1	1
Peritonsillar abscess .	8	7.2	2	2		4
Tracheotomy	6	5.5	1	1	1	3
Spondylitis cervical spine..	3	2.8	2			1
Postoperative thyroidectomy	3	2.8	1	2		
Ludwig's angina . . .	2	1.8	1	1		
Total	110		44	24	6	36

(Courtesy, Ann Surg, Oct, 1938)

the patient upside down, thereby filling the region of the retropharyngeal abscess, in order to establish this as the focal point. Incision of the abscess through the oral pharynx, with the assistance of gravity, sufficed in its drainage, and the baby made a complete recovery.

Giddoll²¹ treated a retropharyngeal abscess, associated with cervical emphysema, of traumatic origin by what he states as "masterful inactivity" and by *hot external compresses*. The patient recovered.

Phillips²² reports 20 cases of suppurative mediastinitis following perforation of the esophagus. One patient recovered without surgical intervention. Of those in whom drainage was effected surgically, 1 patient died as the result of an impacted denture which had perforated into the mediastinum (patient died on day following surgery from double pneumothorax), 1 died as the result of esophagosopic trauma (infected elsewhere) and consequent tracheal and esophageal necrosis and hemorrhage; 1 died of sepsis (patient deferred operation for 2 days). The remaining 16 patients recovered following surgical drainage.

The superior approach to the mediastinum was used *via* the neck, Dakin tubes were employed for irrigation and to facilitate free drainage.

By gradually shortening the tubes, the mediastinal cavities were made to close from the bottom. Average period of healing was 3 weeks.

Pearse, Jr.,²³ made a survey of 110 cases of mediastinitis following cervical infection, in which are included 11 taken from his own experience (Table I).

He concludes that "(1) Gravitation of pus from the neck causes only one-fifth of the cases of suppurative mediastinitis, in this group, however, are found many of the more dangerous infections from visceral perforation. (2) . . . It is found that the suppuration followed the retrovisceral space in 71 per cent, the carotid sheath in 21 per cent, and the pretracheal space in 8 per cent of the cases (3) . . . Operation is indicated, as with surgical intervention the mortality is 35 per cent, as contrasted with 85 per cent when it is not performed."

In studying a surgical approach, the following illustrations should be of material assistance.

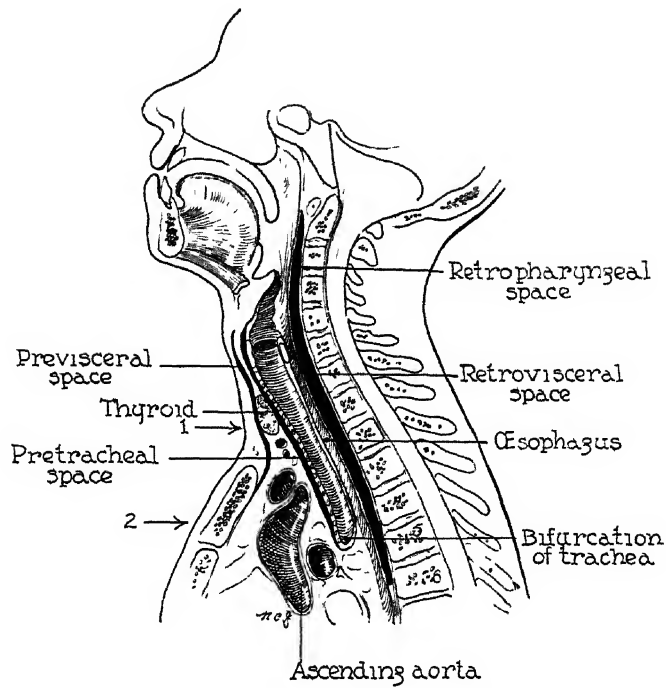


Fig. 26—A longitudinal section to show the cervical spaces. In front is the prevertebral space which ends at the sternum and does not enter the mediastinum. Next is the pretracheal space which conveys infection from tracheal and thyroid gland operations. Behind is the retrovisceral space, the route traveled by pus in 71 per cent of cases of mediastinitis from cervical suppuration. Note that the retropharyngeal space is not separated from it but is only its upper portion. Numerals indicate the level of cross-section, for Figures 27 and 28 of the text. (Herman E. Pearse, Jr. *Annals of Surgery*, Oct. 1938.)

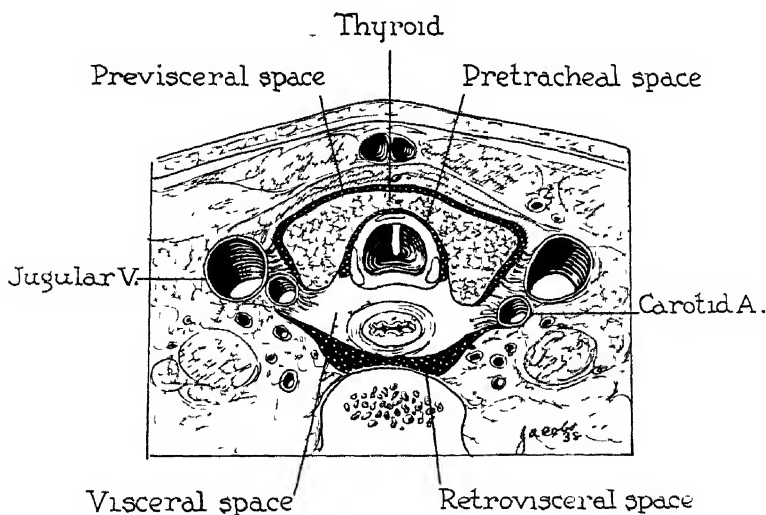


Fig. 27—A cross-section at the level of the thyroid gland. The visceral space including esophagus, trachea and thyroid gland is a compartment surrounded by the pretracheal fascia in front and in buccopharyngeal fascia behind. In its pretracheal portion is a true space. Behind is the retrovisceral space. Note its relation to the esophagus and cervical spine. (Herman E. Pearse, Jr. *Annals of Surgery*, Oct. 1938.)

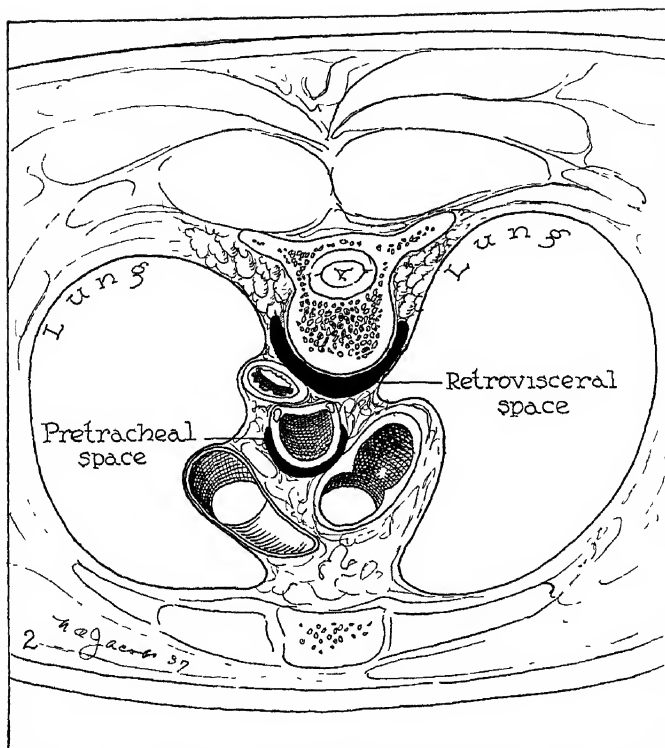


Fig 28—Section in the chest at the level of the fifth dorsal vertebra. The retrovisceral space is in close relation to the pleura (Herman E Pearce, Jr. Annals of Surgery, Oct 1938)

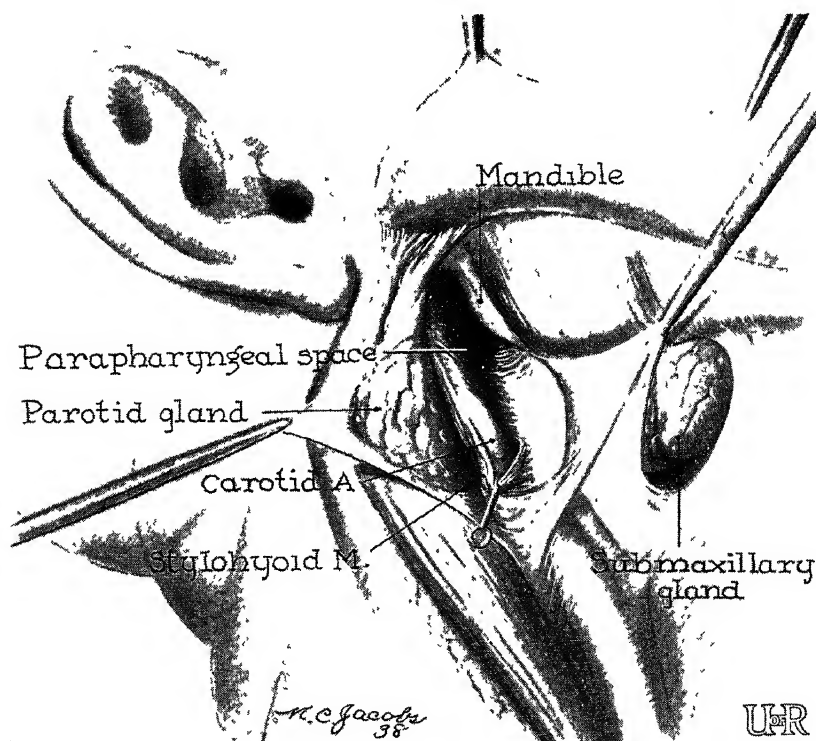


Fig 29—The parapharyngeal space seen from the outside. The fused fascia is left in front to separate it from the submaxillary space. The parotid gland is turned back in this dissection for exposure. This could not be done so widely at operation without facial nerve injury. The parapharyngeal space extends up behind the angle of the jaw and ends below around the carotid artery (Herman E Pearce, Jr. Annals of Surgery, Oct 1938)

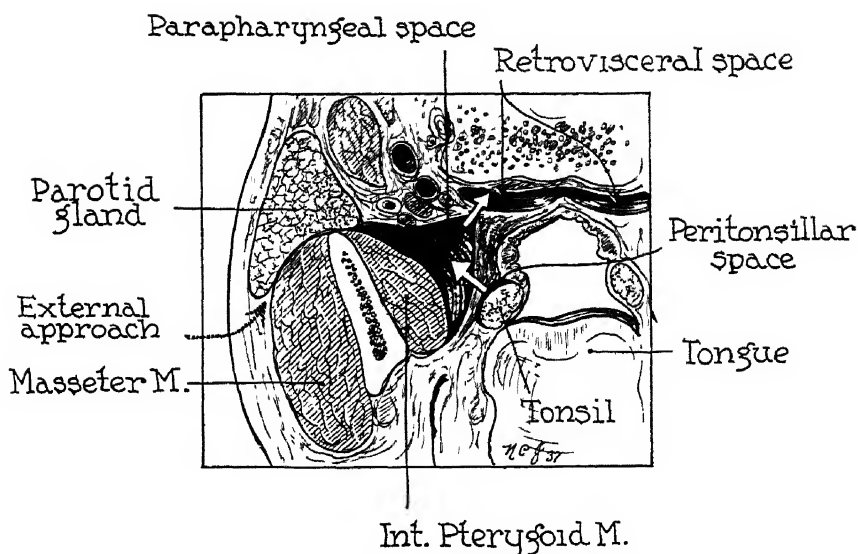


Fig 30—The parapharyngeal space may be invaded from a tonsillar, parotid or retropharyngeal infection. Pus from this space may track down the carotid sheath or rupture into the retrovisceral space to involve the mediastinum (This figure is reprinted through the courtesy of the Journal of the Missouri State Medical Association in Annals of Surgery, Oct 1938)

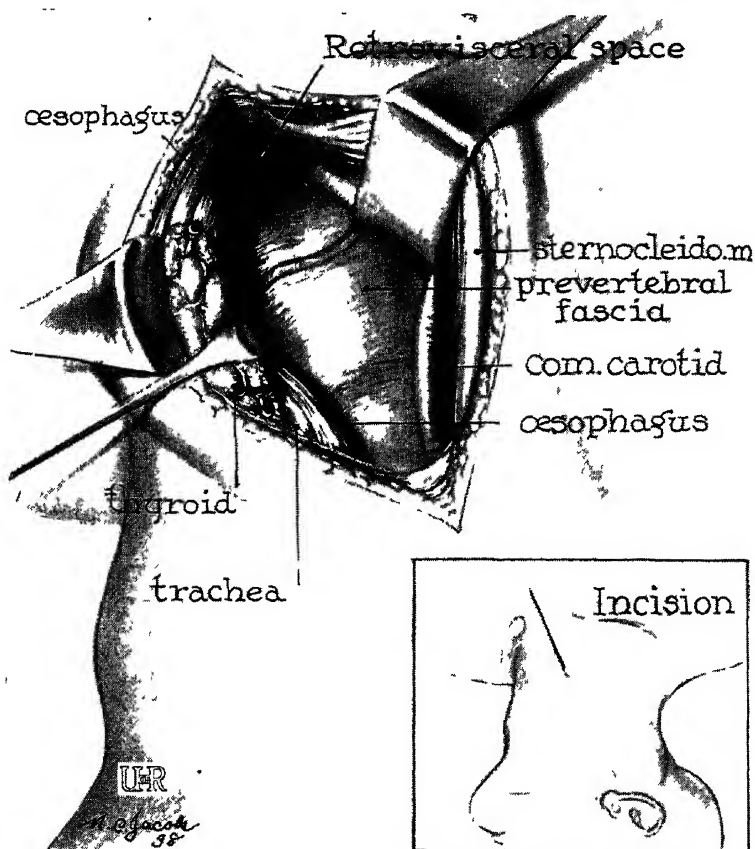


Fig 31—Looking down into the posterior mediastinum through the retrovisceral space, as it is seen at operation. Orientation is easier if the drawing is turned so the head is up. The thyroid gland, trachea and esophagus have been retracted mesially, while the carotid artery, jugular vein and sternocleidomastoid muscle are displaced laterally. This exposure permits visual inspection of the space (Herman E Pearse, Jr Annals of Surgery Oct 1938)

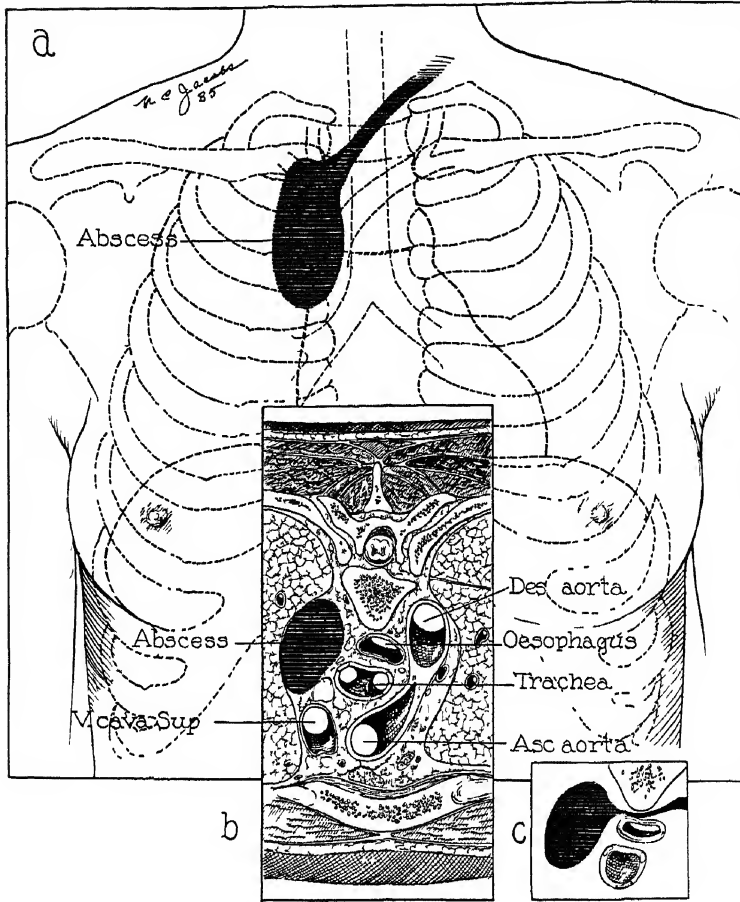


Fig. 32—Case 1. Residual mediastinal abscess 3 months after an acute mediastinitis from esophageal perforation. The location in the vertical plane is shown in *a*, and on horizontal section in *b*. The pinching of the tract between the spine and esophagus is shown in *c*. This caused incomplete drainage of the suppuration and allowed the abscess to persist. (Herman E. Pearce. In *Annals of Surgery*, Oct. 1938.)

Tumors

Cervical Spine—Dysphagia—The esophagus may be said to be freely suspended from the plate of the cricoid cartilage and fixed again only at the diaphragm. Compression of its lumen from without by noninfiltrative masses usually does not interfere with swallowing because of this mobility of the esophagus. Extrinsic neoplasms at any point between these 2 levels result in dysphagia only when they are either extensive in size or infiltrative in character. On the other hand, when a new growth arises, either in the region of the pharyngeal or cardiac ends of the esophagus, then the

mass readily induces symptoms of esophageal obstruction.

Iglauer²⁴ reviews the records of 6 cases of the latter variety reported in the literature in which vertebral protuberances caused difficulty in swallowing. Either the vertebrae of the lower cervical or of the lower thoracic column were involved.

Diagnosis—In the case of the present report, a firm knob was felt on the right side externally, behind the thyroid cartilage, and this knob moved with the spine on rotating the head; the protuberance was seen to be pushing from without the wall of the hypopharynx against

the right arytenoid cartilage; the right pyriform sinus contained saliva. Visualization of the esophagus by barium meal and fluoroscopy revealed obstruction in the right pyriform sinus to the passage of the opaque material. The barium detoured into the esophagus through the left pyriform sinus. A flat plate showed the bodies of the fifth and sixth cervical

A rongeur and chisel were used (by Dr. Joseph Freiberg) in its removal. Post-operative feeding for the first 48 hours was accomplished through a pernasal duodenal tube. Thereafter food was given by mouth without trouble. Convalescence was uneventful. After examining the roentgenograms and a microscopic section of the specimen, the fol-

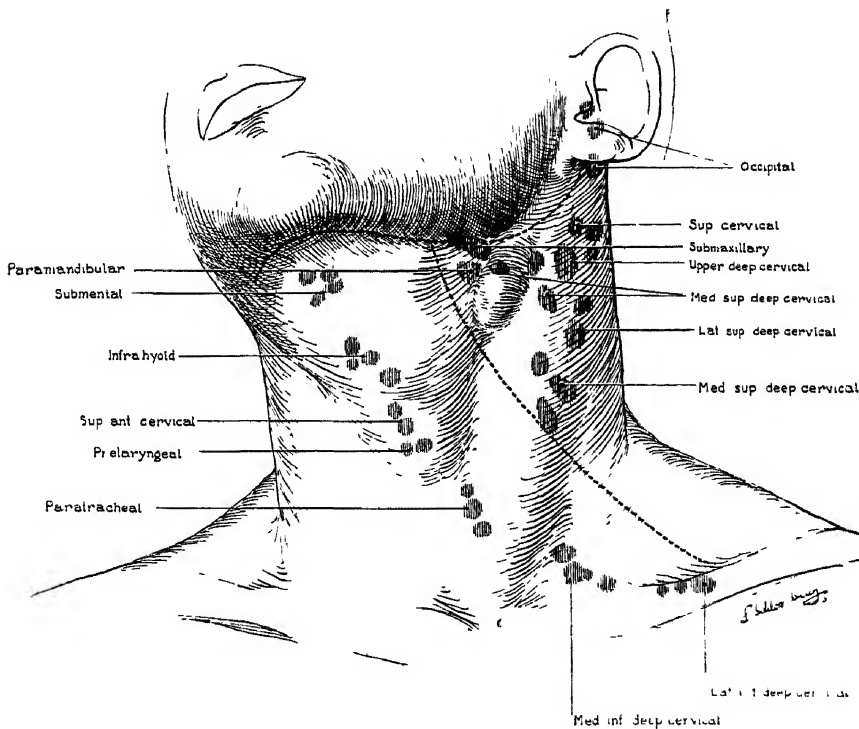


Fig. 33—Distribution of the superficial and the deep lymphatic glands of the neck. The interrupted lines indicate the incisions in the skin (Courtesy, Arch. of Surg., Aug. 1938.)

vertebrae to be united by an exostosis arising from the front of each, the bodies of the sixth and seventh were fused together.

Treatment—According to Iglauder, no surgical intervention had been employed in the 6 cases reviewed by him. In his case, the vertebral column was exposed surgically (anterior sternocleidomastoid—esophageal approach) on the right side and the tumor was located. It was found to be knob-shaped and hemispherical; size $2\frac{1}{2}$ cm wide and 2 cm high

lowing report was received from the Bone Registry of the American College of Surgeons: "I believe this is a hypertrophic arthritis of the spine with the formation of an enormous bridge between 2 vertebrae. The cartilage is a part of the process of enchondral bone formation in the laying down of the big bony bridge."

Examination of the patient 6 months following the operation revealed great improvement in the passage of the swallowed barium, which descended through

both pyriform sinuses (better on the left). There was no recurrence of the tumor.

Metastatic Lymphadenopathy

Treatment—This phase was reviewed last year from a surgical point of view directed at securing adequate microscopic evidence and relieving the patient's biologic burden of destroying and eliminating extensive accumulations of malignant tissue. Such principles are rational, until such time when treatment, either

Statistical tables recorded by Cohn are of interest. Unfortunately, the greater number of cases are under the 10, or even 5-year period, and must be regarded on this basis in any desire to evaluate these statistics. But he concludes: "Enough time has elapsed since operation in a sufficient number of cases to allow the statement that many patients who had carcinoma of the cervical glands are now well" Further, his statement, "in which the condition is operable," disregards a point of view that

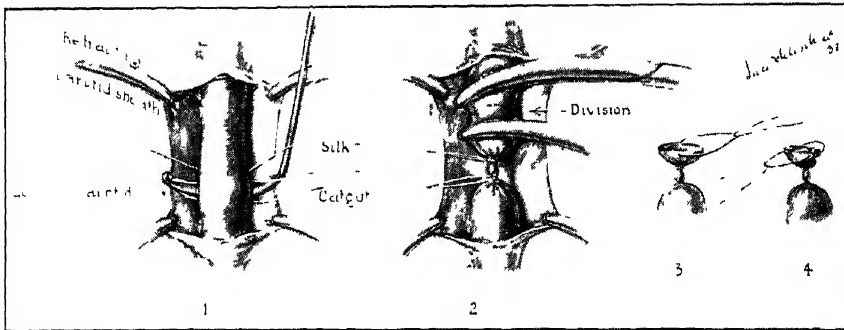


Fig. 34—Mobilization, ligation and division of the left internal jugular vein in the lower third of the neck. (Courtesy, Arch. Surg., Aug. 1938.)

in the prophylactic or active management of metastases, is of specific character.

Consequently, so far as prognosis is concerned, an attitude of helplessness is universally assumed when such lesions are discovered. On the other hand, there are certain reports which take exception to this attitude or opinion. These reports deal mostly with the metastases which attend lip and tongue malignancies. Any surgical approach to cervical metastases should above all else take into consideration the site of the primary growth. It is notorious that pharyngeal and laryngeal malignancies are not the exceptions referred to above. In this respect, Cohn's report²⁵ is pretentiously titled, though the statement just made is included by him.

the presence of a metastasis presupposes a state of inoperability. The illustrations of the lymph node distribution, lines of incision and operative procedure are instructive. The description of the technic is given by Cohn as follows:

"The position of the patient on the operating table is flat on the back with the neck extended. The incision in the skin extends from the mastoid process of the temporal bone to a point about 2.5 cm. below the angle of the lower jaw and from this point continues parallel to the jaw to a point on the opposite side below the mental foramen. A second incision, beginning at the middle of the clavicle, meets the horizontal incision at a point midway between the angle and the symphysis of the lower jaw (Fig. XX). Three flaps are raised by con-

tinuing the incision through the platysma myoides muscle and undercutting. At this time it is well to ligate, preferably with fine black silk, the small vessels which have been previously clamped. After the flaps composed of skin, subcutaneous fat and the platysma myoides muscle have been dissected back, the sternocleidomastoid muscle is divided a short distance above the clavicle, the

left *in situ*. I have always transfixed a third ligature to the distal stump of the vein, using a straight intestinal needle threaded with fine black silk (Fig. XX).

"The common carotid artery is then exposed quickly by dividing the carotid sheath. (Fig. XX). The carotid sheath is stripped upward, the bifurcation of the carotid artery thus being brought into view. Rather than to attempt liga-

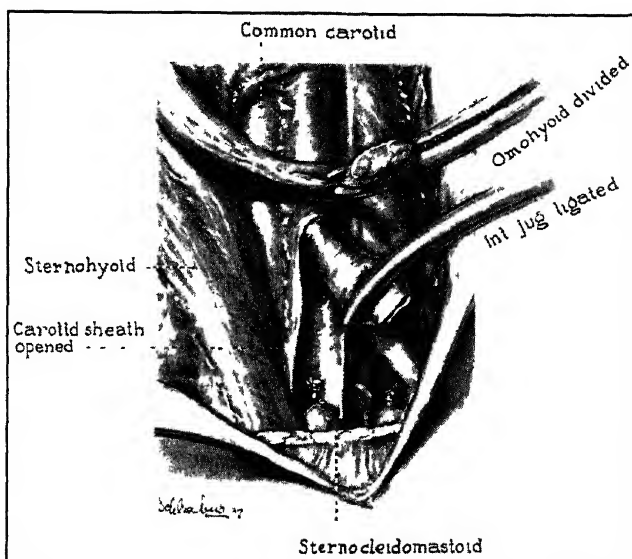


Fig 35—Ligation and division of the internal jugular vein completed
(Courtesy, Arch Surg, Aug 1938)

external jugular vein first being divided and ligated. The division of the sternocleidomastoid muscle brings into view the omohyoid muscle, which is in turn divided at the level of the division of the sternocleidomastoid. The internal jugular vein is now visible and readily accessible. The sheath of the vein is divided, and a section of the vein 4 cm in length is mobilized. A ligature of double zero chromic catgut is placed around the vein with an aneuroism needle. A second ligature, of fine black silk, is placed just above the catgut. Both ligatures are tied, and the vein is doubly clamped above the second tied ligature and divided between the clamps, the upper clamp being

tion of the branches of the external carotid artery at this stage it is preferable to continue the excision along the anterior margin of the omohyoid muscle as far as the hyoid bone, clamping, dividing and ligating the superior thyroid vessels as they come into view, at the same time excising the lymphatic area anteriorly as far as the sternohyoid and the thyrohyoid muscle, removing the paratracheal, prelaryngeal, superior anterior cervical and infrahyoid lymphatic glands. The omohyoid muscle is then excised near the hyoid bone.

"Next is the excision of the submental lymphatic glands, and in order to make this complete it is well to expose the

periosteum of the lower jaw and to carry the excision of glands to the capsule of the submaxillary salivary gland on the opposite side. When the primary carcinoma is situated on the anterior third or the tip of the tongue or on the lower lip, it is well to study a frozen section of the lymphatic gland between the opposite submaxillary gland and the

artery being thus again exposed. The branches of the external carotid artery are divided between clamps and ligated. When the primary carcinoma involves the base or middle third of the tongue, the lymphatic glands near the bifurcation of the carotid artery are sometimes extensively involved and adherent to the carotid sheath. Even so, it is rarely

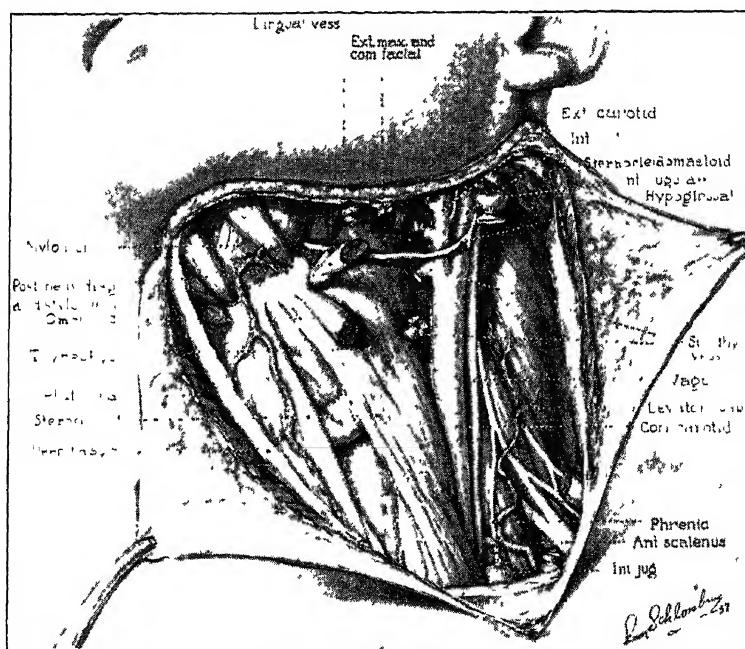


Fig. 36—Wound after the complete block dissection of the cervical glands, showing the extent of the surgical excision. (Courtesy, Arch. Surg., Aug. 1938.)

jaw, as metastasis to this gland indicates bilateral involvement. The endotherm needle may be used for the greater part of the dissection and especially for excising the submental glands and for the dissection along the lower jaw.

"The facial vein and the external maxillary artery are ligated and divided, and by retraction on the mylohyoid muscle the submaxillary salivary and the sublingual glands are readily excised up to the mucous membrane of the floor of the mouth. The submental and the submaxillary glands are gently rotated posteriorly, the bifurcation of the carotid

artery being thus again exposed. The branches of the external carotid artery are divided between clamps and ligated. To facilitate the excision of this deep group of cervical glands it is often advisable to excise or divide the posterior belly of the digastric muscle.

"The next procedure is the ligation and division of the artery and the vein to the parotid gland and the division of the sternocleidomastoid muscle near the mastoid process. The upper deep cervical and the occipital glands are then accessible and are removed up to the base of the skull. The internal jugular vein is clamped and ligated a short distance below the jugular foramen. It is

usually safer to use an electric cautery in excising the occipital and the superior cervical glands if they appear grossly involved. The excision of glands is continued distally from this point, and the deep cervical glands behind the excised internal jugular vein are included in the excision. At this time procaine hydrochloride is injected into the neural branches to the scalenus muscles and the levator scapulae muscle, and the supraclavicular glands (median and lateral inferior deep cervical) are excised to the junction of the internal jugular and the subclavian vein and posteriorly and laterally to the scalenus muscles (Fig. XX). The clamps controlling the small bleeding points are quickly ligated; sometimes a triangular area of skin is excised where the 2 incisions meet, and the wound is rapidly closed to within 2 cm. of the clavicle by approximating the skin with interrupted sutures of fine black silk. Although there is considerable serosanguineous drainage for about 24 hours, primary healing occurs almost without exception."

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OTOLOGY

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EXTERNAL EAR

Prominent Ears

Correction of prominent ears by surgery is of importance not only from the standpoint of the deformity, but also from the psychologic viewpoint, according to J S Davis and E. A Kitlowski¹ The malformations known as "lop or bat

ears" are congenital in origin are also discussed by D W. MacCollum² who recommends that the plastic repair be carried out in childhood before the patient suffers embarrassment from a deformity which is so readily correctable

Prominent ears are fairly common, and are usually congenital The deformity is most often bilateral, and may be more

marked on one side than on the other. Abnormally prominent ears may be divided into 2 general groups; first, those in which the ear is of normal shape, but is attached to the head in an abnormal position; second, those in which there is an abnormality of the ear itself. After successfully restoring prominent ears to normal position, the appearance of the patient is vastly improved; the mental aspect is entirely changed for the better, and many adults are able to obtain suitable employment from which they had been barred on account of their bizarre appearance.

Many operative procedures have been described for the correction of the lop ear but MacCollum's opinion is there are only 3 methods that meet the fundamental requisites for a satisfactory repair. These requisites are that: (a) The angle formed between the ear and the mastoid region must be reduced to at least 30 degrees, (b) the convolutions of the cartilages must be shaped to form an antihelix and a scapha, both of which are absent in the lop ear, and, (c) the skin incision must be hidden behind the ear so that it is not readily noticeable.

In correcting a lop ear the surgeon must plan to make the curvature of the antihelix less acute and the scapha slightly wider than in the normal ear. For the purposes of orientation the position of the planned antihelix is first marked off on the anterior surface with brilliant green solution or sterile Bonney's blue paint (Components of Bonney's blue paint are brilliant green, 87 Gm, crystal violet, 87 Gm, 95 per cent alcohol, 10 ounces; distilled water, 10 ounces.) Along the line, punctures are made through the entire ear with a needle carrying the paint, so that the curvature of the new antihelix will be projected as a line of dots in the skin on the back of the auricle. These dots

will then outline 1 side of an ellipse. The remainder of the ellipse is marked off so that one-half of it lies on the posterior surface of the auricle and the other half over the mastoid region. Procaine hydrochloride and epinephrine are injected into the skin over the front and back of the ear so as to facilitate the dissection of the cartilage and to prevent excessive bleeding. The ellipse of skin, previously outlined on the posterior surface, is now removed.

An incision is next made through the cartilage along the line demarcated by the ink dots previously produced by the perforating needle. Great care should be taken to avoid buttonholing the skin on the anterior surface. Through this incision the cartilage is then freed carefully from the skin on the anterior surface so that the edge of the outer portion of cartilage can be inserted under the edge of the proximal portion. The cut edge of the inner or proximal cartilage will then form the ridge of the new antihelix. As the 2 parts of the cartilage slide over each other it is found that the ear will begin to assume a normal position. In most cases the outer or distal cartilaginous plate, which is now to form the structural foundation of the scapha, will be too wide. For this reason a sickle- or crescent-shaped portion of this outer cartilage must be removed before the cartilaginous convolutions simulate a normal appearance. It follows that the ear which protrudes markedly will require the excision of a wider strip of cartilage than one that is less prominent. When a satisfactory correction has been obtained, the 2 layers of cartilage are sutured to each other by interrupted sutures of 000 chromic catgut. To insure their anchorage to the head, both are sutured as a layer to the postauricular fascia of the scalp. This brings the skin edges together so that they may be closed with

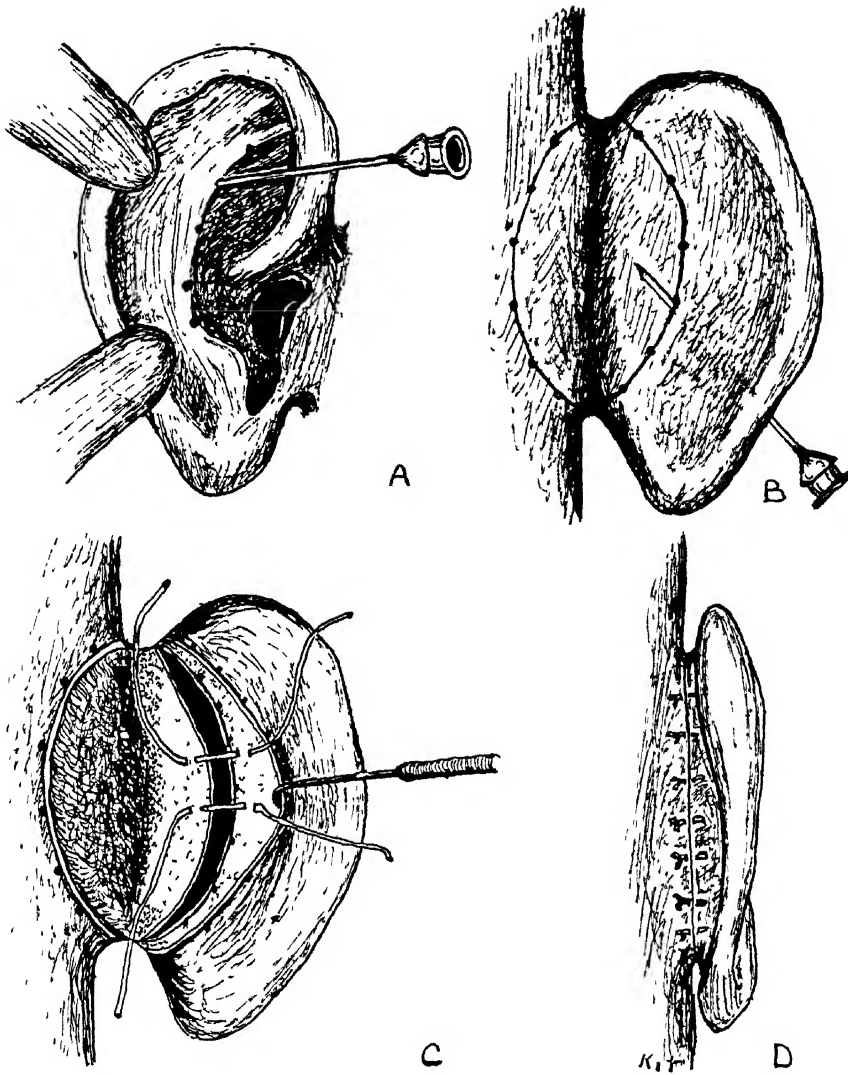


Fig 37—Schematic drawings showing the steps in the operation for the replacement of prominent ears. *A*, The ear is placed in its normal position against the head and the upper and posterior limits are marked on the scalp with a hypodermic needle dipped in brilliant green, 5 per cent in alcohol. Note 2 punctures above the ear and 1 behind. With the ear in this position the undeveloped antihelix will re-form sufficiently to indicate the line of proposed reconstruction. Along this line with a hypodermic needle dipped in the brilliant green solution, punctures are made completely through the ear and about 1 cm apart. *B*, Shows the puncture marks and the needle emerging on the posterior surface of the ear through one of them. The needle shown in the drawing is comparatively much larger than that actually used which is 24 gauge and 1 inch long. The points of perforation are connected with a line of brilliant green and while the solution is still damp the ear is pressed against the head and a contact line is made. This line is freshened with the green solution and the ends are carried forward and joined, making an elliptical-shaped pattern. The area of skin thus outlined is that which is to be removed. *C*, The skin has been removed. The marks of the perforations in the skin can be seen. The second line of green-stained dots are those left in the cartilage by the needle punctures through the ear. The area from which the cartilage was excised, which conforms to the curve of these perforations, is shown. The cartilage spring has been broken. Two sutures of catgut of the type used to turn in the cartilage edges to form the antihelix can be seen placed in the perichondrium. *D*, The ear assumes normal position and the skin is closed with on-end mattress sutures of horsehair. (Davis and Kitlowski. Surgery.)

a continuous subcuticular stitch of 000 plain catgut.

In the postoperative dressings sterile seasponge or fine gauze is packed into the concavity of the auricle, which are held firmly in place by an elastic net, band or adhesive. It is important that these bandages exert enough pressure to control all the oozing but not enough to endanger the viability of either the skin or the cartilage. The first dressing is removed on the third or fourth day for inspection of the color of the ear. If the procedure has been done with gentleness and if the skin has not been undermined too extensively, the ear should be of normal color. If there are any areas which are dusky or blue, the ear must be examined for hematoma. If a hematoma has formed it must be expressed completely to avoid a slough of the skin overlying it.

Meningitis

According to O. R. Kline³ meningitis has been and in fact still is the most dreaded complication of suppuration of the temporal bone. Formerly cures were rare and treatment nonspecific for in a period of 35 years the literature reported but 66 cases of recovery, approximating a 97 per cent mortality. In 1936 the first report of a cure of streptococcic meningitis was reported in the French literature and since that time the statistics have been preponderantly of cures due to the use of chemotherapy, prontosil (the hydrochloride of a 4-sulfamido-2', 4'-diaminoazobenzene). Kline found that in the literature more than 100 patients with hemolytic streptococcic meningitis were cured by this drug during the past year, whereas the mortality was more than 95 per cent before this drug was available. Sufficient evidence has accumulated to prove that it is a valuable drug when used intelligently. When used in

the treatment of otitic infections it should in a certain number of cases prevent the development of a condition in the mastoid which requires an operation, but at no time should faith in the virtues of this drug influence surgical judgment. Adequate surgical treatment of the mastoid should always be carried out when indicated to prevent meningitis and other complications. Early symptoms of meningeal irritation demand an immediate mastoidectomy, with exposure of the dura. In the presence of meningitis, after the focus of infection has been eradicated, a supportive and conservative method of treatment is followed.

From 1924 to 1936, N. Silverthorne and A. Brown⁴ treated 93 patients with meningitis due to the hemolytic streptococcus. These patients were treated by 1 or more of the following procedures: *spinal drainage*, *intravenous dextrose-saline injections*, *scarlet fever antitoxin* and *mastoidectomy* when indicated. There was only 1 recovery. Nine patients with streptococcic meningitis during 1937 have been treated with *sulfanilamide*, a continuous *intravenous injection of dextrose-saline* and daily *spinal puncture with drainage*. Mastoidectomy was performed in 6 of the 9 cases in which mastoiditis was present. Five of these 9 patients have recovered. It is the authors' belief that sulfanilamide has been chiefly responsible for the recovery of these patients.

Several papers were read at the June 17 meeting of the Société médicale des hôpitaux of Paris in which 10 cases of streptococcic meningitis successfully treated with sulfanilamide were reported.⁵ In the first paper Dr. Brulé and his associates reported a case of acute optochiasmatic arachnoiditis with streptococcic meningitis, which had developed after the lesion of suppurative tonsillitis had evacuated its contents spontaneously.

about 3 weeks before the patient's admission to the hospital. During the first stage the only complaint was a severe headache. There was a slight rise of temperature, but ocular examination revealed the typical appearances of acute optochiasmatic arachnoiditis secondary to the tonsillar infection. At this time lumbar puncture showed 240 leukocytes per cm. In the second stage (3 days after admission) the symptoms and signs of diffuse meningitis became marked. Cultures of the fluid obtained by lumbar puncture showed the causative organism to be the hemolytic streptococcus. Sulfanilamide was immediately given, 65 Gm by mouth and 3 intraspinal injections of 0.2 Gm. over a period of 28 days. The authors expressed the opinion that the intraspinal method of administration had been more efficacious than the oral method. During the third stage a marked improvement of the arachnoiditis was noted. This is unusual, because as a rule this condition ends in complete loss of sight.

The second paper was by Dr. René Martin of the Institut Pasteur, who stated that the mortality rate of streptococcic meningitis had until recently been 97 per cent. He had given sulfanilamide to 3 children with the disease, all of whom recovered. In addition to these 3 children observed at the Institut Pasteur, 3 others with streptococcic meningitis of otitic origin had been successfully treated with sulfanilamide. The drug should be given in large doses and the administration continued for at least several weeks after apparent recovery to prevent recurrences. During the first few days sulfanilamide is given both by mouth and intraspinally. For oral administration, adults are given from 8 to 10 Gm and children 0.15 Gm daily per kg. of weight. On account of rapid elimination of the drug, it is advisable to

give it every 2 hours during the day and every 3 hours during the night. It is given intraspinally during the first days of the illness. After from 10 to 20 cc. of spinal fluid, according to the age of the patient, has been withdrawn, an equal quantity of an 0.85 per cent solution of sulfanilamide, previously heated to body temperature on a water bath, is injected. The doses for intraspinal use are increased or decreased according to whether the concentration of the sulfanilamide in the spinal fluid is superior or inferior to 4 mg. per 100 cc. of the cerebrospinal fluid. The higher the concentration, the more rapidly does recovery take place. The permeability of the meninges toward sulfanilamide varies with each patient; hence the necessity of adjusting the doses for intraspinal use according to the concentration of sulfanilamide in the cerebrospinal fluid. Dr. Martin expressed the opinion that the administration of sulfanilamide by intraspinal route was the chief factor in the success of treatment in his cases of streptococcic meningitis.

The third report was submitted by Prof. Robert Debré and his associates. Before using sulfanilamide, they had observed 20 similar cases of meningitis with but 1 recovery. The 3 patients to whom they gave sulfanilamide were children 6, 4 and 9 years old and in all the meningitis was of otitic origin. These authors employed both the oral and the intraspinal method of giving the drug. For oral administration, doses as high as from 3 to 5 Gm daily must be given even to children, and they must continue to be given for 3 weeks after apparent recovery. For intraspinal administration they used an 0.85 per cent solution, of which a minimum of 15 cc. should be injected if the concentration of sulfanilamide in the spinal fluid is not inferior to 4 mg per 100 cc. When the concentration is reached or when the spinal

fluid is sterile and contains very few leukocytes, the intraspinal method is discontinued. The spinal fluid became sterile within 48 hours after the beginning of treatment. The complications noted, so far as the effects of the drug are concerned, were cyanosis, at times very marked at the onset but decreasing noticeably even though use of the drug was continued, a rather persistent cough and in 1 case a drop in the red cell count to 1,730,000.

Although the number of patients who have recovered from otitic meningitis caused by the beta hemolytic streptococcus after treatment with sulfanilamide appears to be growing rapidly, F. W. Smith, *et al.*,⁶ report what they believe to be the first time a case of meningitis caused by an anaerobic beta hemolytic streptococcus with recovery under sulfanilamide therapy. Oral administration of the drug was relied upon exclusively with the exception of the first

streptococci produced acute fulminating meningitis with associated septicemia, which was fatal in from 18 to 48 hours. The treatment of 46 rabbits with the drug, begun 4 hours after inoculation, resulted in recovery in 9 and prolongation of the lives of most of the remaining animals. In monkeys the meningitis, unaccompanied by septicemia, was fatal in about 72 hours. In 12 animals, the injection of the drug 24 hours after inoculation resulted in recovery of 7. In the pneumococcal cases the drug was not curative but did in many instances prolong the lives of the animals. Kolmer believes that the therapeutic action of sulfanilamide, given orally, subcutaneously and intraspinally, appears to depend on the promotion of phagocytosis of streptococci, which is probably the result of some bacteriostatic effect resulting in the production of less antiphagocytic substance. A scale of suggested doses to be administered is as follows:

Approximate Weight Pounds	Oral Alone, Tablets		Intramuscular Alone, Cc of 0.8% Solution		Combined Oral and Intramuscular			Intra-spinal
	Every 6 Hours	Total 24 Hours	Every 6 Hours	Total 24 Hours	Oral, Every 6 Hours	Intra-muscular, Every 6 Hours	Total 24 Hours	Every 12 Hours 0.8% Solution
20	1/2	2 (0.6 Gm.)	12	50 (0.4 Gm.)	1/2 tablet	10 cc	0.68 Gm.	5 cc (0.04 Gm.)
50	2	8 (2.5 Gm.)	50	200 (1.6 Gm.)	2 tablets	25 cc	2.70 Gm.	10 cc (0.08 Gm.)
100	3	12 (3.5 Gm.)	75	300 (2.4 Gm.)	3 tablets	50 cc	4.00 Gm.	15 cc (0.12 Gm.)
Adults	4	16 (5.0 Gm.)	100	400 (3.2 Gm.)	4 tablets	50 cc	5.40 Gm.	20 cc (0.16 Gm.)

few days when prontosil was given intramuscularly. The authors emphasize the importance of anaerobic culture procedures in routine bacteriologic studies.

In an attempt to throw some light on the action of sulfanilamide and its derivatives, J. A. Kolmer and his associates,⁷ carried out experimental work on animals. In rabbits the intracisternal inoculation of virulent beta hemolytic

Under favorable conditions the dose may be reduced after from 3 to 5 days, but oral administration is advised for at least 2 or 3 weeks as a safeguard against a recrudescence of the infection.

M. Molhant⁸ states that the term serous meningitis was employed first by Quincke to characterize the excessive production of cerebrospinal fluid with accumulation in the cerebrospinal spaces.

Before taking up the different forms of serous meningitis, the author discusses the biologic physiology of the cerebrospinal fluid. He emphasizes the importance of the biologic equilibrium of the cerebrospinal fluid on the stimulation of the hypothalamic sympathetic centers and the rôle of the cerebrospinal fluid in the regulatory mechanisms of the humors. He shows that the clinical aspects of localized serous meningitis, at least in its simple forms, are the manifestation of an organofunctional pathogenic complex. The meningeal cyst is a sequel of a subacute inflammation of the brain and meninges. The treatment of choice is the intradermal tuberculin desensitization.

Discussing the generalized cerebral serous meningitis, he takes up first the purely toxic forms, which are caused essentially by the noxious action of certain endogenic toxic substances. Hypertonic solutions of dextrose in massive doses, repeated for several days, have a remarkable curative action in the acute cases. The second type of generalized meningitis discussed by the author is the form that is due to toxic sensitization either by a medicinal or by an infectious factor. The reported histories indicate intoxication with phenobarbital, alcohol, gold salts and so on, the presence of chronic evolutive tuberculous processes or the combination of these medicinal and infectious factors. In these cases the administration of hypertonic solutions of dextrose constitutes the treatment of choice during the acute periods. In the chronic forms repeated lumbar punctures, decompressive craniectomy and other intracerebral interventions have been recommended. Roentgen treatment has also been recommended because under its influence the production of cerebrospinal fluid is decreased. The author utilized with good success intradermal

tuberculin desensitization. This treatment is simple, inoffensive and at the disposal of the general practitioner. By its para-allergic action it dynamizes and regulates the apparatus of disturbed biologic regulation of the dyscrasic organism. It has a desensitizing action. By its specific allergic action it contributes also to the cure of the tuberculous lesions.

DEAFNESS

The hearing problem presents a real challenge to medicine, according to C. E. Kinney,⁹ who finds that lay organizations with its societies for the hard of hearing, commercial firms who manufacture hearing aids and audiometers, governmental agencies and the medical profession are all vitally involved. A comprehensive program includes measures calculated to prevent deafness, conserve hearing and, finally, the rehabilitation of the patient.

Hearing impairments are divided into 2 classes, those having their inception from birth to the end of a person's educational period (21 years), and those having their inception after 21 years of age. The relative incidence of cases in these 2 age groups is approximately 50 per cent in each group. Accurate figures are not available. As to their relative importance, according to Kinney, there is no question—because of the social and educational factors involved—the early life group is by far the more important.

Later-life deafness can be further divided into 2 groups, approximately 70 per cent being either ostosclerosis or senile deafness. Of these 2 types, to date little has been done to either prevent or ameliorate this class of hearing impairment. Of the remaining 30 per cent they consist mainly of catarrhal deafness with the occasional case of otitis media and eighth nerve tumor. These 3 types

of deafness can be successfully treated and it behooves all physicians to see that these cases are properly diagnosed and proper treatment instituted as early as possible.

Early life hearing impairments may be divided into 3 groups, as follows: (1) Those occurring before birth, (2) those occurring as a complication of a contagious disease, and (3) those due to otitis media of a nonspecific origin.

Hearing impairments occurring as a complication of contagious diseases constitute a large majority of early life cases. The general practitioners and pediatricians working in conjunction with the public health officials are constantly reducing the incidence of these cases. However, further reduction can be accomplished. Twenty-five years ago, diphtheria, typhoid fever, infantile paralysis and epidemic spinal meningitis contributed to a large share of our hearing cases. Today these diseases are rare. No one but the medical profession can claim credit for this fact.

Scarlet fever, measles, and mumps are still responsible although the severity of these cases is definitely less and as a consequence ear complications are less frequent. It is possible to further reduce the frequency of hearing during the convalescence stage. It has been the author's privilege to see several cases of hearing impairment during the convalescence from measles, which impairment was practically eliminated by prolonging the bed rest and forcing fluids on these patients. One can properly ask how can the general practitioner examine these patients as to their hearing. The audiometer is out of the question and the so-called watch tick test is useless. The spoken voice test is of great value providing that 1 ear is tested at a time. Testing 1 ear at a time can only be accomplished by using a Barany noise apparatus in

the ear not being tested. It is most important to remember that a person can lose up to approximately 40 per cent of hearing in 1 ear without being cognizant of the fact and unless the doctor examining the ear tests only 1 at a time this loss may be missed by him.

The third group of early life hearing impairments are from nonspecific otitis media. The incidence of these cases is probably the same as it was 25 years ago. This incidence can be reduced by at least 80 per cent if the medical profession considers 2 facts; namely:

1. Practically all cases of nonspecific otitis media are caused by the patients themselves forcing virulent bacteria into the middle ear.

2. Most of the hearing impairment occurs after the active infection has stopped.

The nose should always be blown with both nostrils open and the secretions from the nose drawn back into the pharynx. The second point is that permanent impairment of hearing caused by an acute attack of otitis media occurs from 3 to 6 weeks after the discharge has stopped. This is due to the formation of adhesions around the 3 ossicles in the middle ear. These adhesions are prevented by active massage of these parts through both the eustachian tube and the external ear canal. A patient having had an actively discharging middle ear should not be released from medical care until at least 2 months after the discharge has stopped and the hearing in that ear is essentially the same as it was before the disease started.

TINNITUS AURIUM

Most cases of tinnitus are subjective in character.¹⁰ There are, however, unusual occasions in which the noise may be demonstrated to an observer. Head

noises may arise from conditions within the ear and in the immediate neighborhood of the ear. In practice the most persistent and annoying forms of tinnitus are usually seen in connection with disease of the internal ear and its central pathways. Tinnitus due to conditions within the external auditory canal and the middle ear are apt to be much less annoying and much more amenable to treatment. In the neighborhood of the ear transmitted noises from arteries, veins or aneurisms are occasionally observed. The use of drugs such as acetylsalicylic acid may produce tinnitus without apparently any permanent or demonstrable effect on the hearing.

The description of the sounds varies from low, rushing, murmuring sounds usually assigned to disease in the middle ear to high pitched, hissing, whistling, ringing noises generally thought to be due to difficulties in the internal ear. From this type of head noise to a type characterized by distinct musical character is only a short step. Such noises may be designed as whistling, ringing, bell-like in character. One step further carries one into the realm of noises that begin to partake of hallucinations. A patient will say that an old melody recurs over and over again, perhaps some song not heard since early childhood. The last step is, of course, distinctly hallucinatory in character. Voices and other sounds are heard and associated with mental disturbances of a profound character.

Again it is not easy to say how much the so-called nervous constitution has to do with these noises. Certainly, a persistent tinnitus may make the most self-contained person nervous and, on the other hand, it should not surprise any one that the highly strung person would be apt to exaggerate the distress he experiences.

It is therefore plain that the patient's description of the noises and the degree of reaction to them must in some measure be related to the nature and location of the disease area as well as be influenced by the temperament of the sick person. The patient is of a nervous character. Her complaint, with its intermissions, is such that it could be due to some disturbance in the end organ of hearing and its central pathways. She also has had a hypertension and, while the blood pressure is lower now than it was, there still may be changes of a vascular character in the brain sufficient to produce the symptoms. There is no statement as to the absence or presence of a hearing defect. The presence of a hearing defect, especially a severe one, might help to locate the lesion in the cochlea. It is just such deafness of an auditory nerve type that produces tinnitus of the more severe and persistent kind. From time to time also, tinnitus of a stubborn and troublesome character may precede by many years the onset of such a deafness.

Experience states that treatment of the type of tinnitus described is apt to be without benefit. Psychotherapy, encouragement of the patient to accept her condition with as much philosophy as possible and the avoidance of fatigue and nervous strain as well as the use of mild sedatives are all indicated. As much as possible one should attempt to discover the cause and by so doing influence for the better this most aggravating complaint.

E. A. Bredlau¹¹ reports 3 cases of objective tinnitus and reviews similar cases described in the literature. Objective tinnitus may be either vascular or muscular in origin. Spasmodic contractions of the eustachian tube are the chief causative factors in the muscular type of objective tinnitus; the immediate cause is the separation of the moist sur-

faces of the eustachian tube. Hysteria and neurasthenia have been hypothesized as predisposing or contributing factors. The vascular type of tinnitus is caused by the preternatural transmission of arterial or venous impulses to the ear by (1) aneurisms, including arteriovenous aneurisms, both intracranial and extracranial, (2) hypertension, (3) vascular tumors of the brain and the ear, (4) coarctation of the aorta, (5) severe anemias, (6) pregnancy, (7) acute inflammatory disease of the ear and (8) vasomotor and endocrine disturbances.

OTOSCLEROSIS

F R Nager and J S Fraser¹² encountered bone formation in the scala tympani in only 6 petrous bones out of 62 cases of otosclerosis. Analysis of these cases indicates that the extent of the disease of the bone in the labyrinthine capsule of all these patients was large and not circumscribed but diffuse and including both windows. The bone marrow contained many dilated blood vessels, newly formed connective tissue and numerous osteoclasts. These patients were almost totally deaf, which condition is easily explained by the obliteration of both windows. The scala tympani was almost filled up in the more advanced cases. With the exception of 1 case, the lowest end of the scala tympani was filled up, including the cochlear aqueduct. In general the inner ear of these petrous bones did not show distinct signs of old inflammation, with the exception of a darker staining of endolabyrinthine fluids. They cannot accept the idea of a former labyrinth infection as a cause of these alterations but are inclined to believe that the otosclerotic process in the labyrinthine wall produces alteration or irritation of the endosteal layer and perilymphatic space which leads to circum-

scribed fibrous and bony production in the scala tympani. The otosclerotic process will penetrate even this newly formed bone. Such formation of bone in the inner ear has been found only in otosclerotic diseases of the labyrinthine capsule, whereas all other disorders of bone do not lead to these alterations.

Treatment—M. A. Goldstein¹³ has used $\frac{1}{64}$ grain (0.01 Gm.) of *thyroxine* in 42 instances of otosclerosis in young persons, following the technic of Gray. The tablet of thyroxine placed on a watch glass is dissolved in 4 drops of warm sterile distilled water and is injected through the drum membrane directly into the cavity of the middle ear so that it may be in contact with the promontory and oval window. The patient's head is inclined to a completely lateral position for the ear to be anesthetized with from 15 to 20 drops of aniline oil-cocaine solution. The solution is dropped to the fundus of the canal and is allowed to remain there for 5 minutes, when it is carefully swabbed out. The insertion of the hypodermic needle for injecting the thyroxine is at the point half way between the tip of the malleus handle and the posterior rim of the annulus tympanicus. Immediately after the injection, with the patient in an erect position and with his head thrown well backward, the patient is directed to keep the mouth open wide for 3 minutes, thus preventing part of the injected fluid from escaping down the eustachian tube. Following the injection, the patient is instructed to remain quiet for from 20 to 30 minutes and is further cautioned not to be too active for the rest of the day. The thyroxine treatment consists of 4 consecutive injections made alternately in the right and the left ear at intervals of 1 week. The selection of patients who may be best qualified to receive such treatment is based largely on one's ability

to make a diagnosis of clinical otosclerosis. Patients more than 30 years of age usually are less satisfactory subjects for the treatment, either because of their age or because of the long duration and progressive character of their defective hearing. Of the 42 patients subjected to thyroxine treatment, 23 have shown definite improvement in hearing capacity and in some cases cessation or reduction of tinnitus and a general clarification in the perception of speech, and 10 show slight improvement by comparison of audiograms before and after injection; but this was not stabilized in the final audiograms 6 months or more later. In 9 no improvement was noted following treatment. In no case was there any decrease in hearing following these injections.

A new technic for the improvement of hearing of patients with otosclerosis is offered by J Lempert¹⁴. It is a delicate, highly technical surgical procedure designed to create a fenestra in the bony capsule of the external semicircular canal and to provide a mechanical means of keeping this newly created fenestra permanently open. To obtain the desired results it is essential that every step in this technic be patiently and skillfully executed in its minutest detail. To bring this operative procedure to a successful conclusion it is absolutely essential that every surgical step be performed in the exact order described. Each step in this technic is the foundation for the next step, and unless each step is concluded successfully, the next step and therefore the rest of the operation are doomed to failure. This surgical technic should not be attempted by any young otologist unless he is especially trained for surgical measures of this type. Any otologist with a keen knowledge and understanding of the minutest details in the anatomy of the temporal bone, resulting from a large and

varied personal experience in operations on it, will master this technic without any difficulty after seeing it carried out.

The endaural, antauricular approach to the temporal bone is employed for the following reasons:

1. The tympanomeatal cutaneous membrane which is used to cover the defect can be obtained only when the endaural, antauricular approach to the temporal bone is employed. This was described by J. Lempert¹⁵ previously.

2. To avoid the risk of postoperative infection, in addition to applying the strictest rules of asepsis, it is necessary to limit the surgical attack to the tissues directly concerned and thus reach the objective with the least amount of sacrifice of tissue. This is best accomplished by employing the endaural, antauricular approach.

3. Better visibility and accessibility of the desired surgical field are obtained by this approach.

4. The employment of the endaural, antauricular approach is followed by a convalescence involving the least possible social and economic inconvenience to the patient.

5. Cosmetically, the endaural, antauricular approach results in a status as near as possible to that preceding the operation.

Lempert has operated on 23 patients with otosclerosis by the described technic. In 19 cases a good practical improvement in hearing was obtained and maintained. In 4 cases in which operation was performed in spite of poor existing bone conduction, no improvement in hearing was obtained.

This surgical technic was carried out and all the postoperative dressings made under the strictest rules of asepsis. In no case was there a postoperative infection of the tympanic cavity, the mastoid cavity or the labyrinth.

Of the 23 patients operated on, the newly created fistula in the external semicircular canal remained open in 22. In 1 case the fistula began to show signs of closure at the end of 10 days and was completely closed at the end of 3 weeks. The author believes that in the

22 patients in whom the fistula remained open it will remain permanently open. His experience has shown that when regeneration of bone takes place in a newly created fistula, it does so immediately, and clinical evidence substantiating this fact may be observed after the first deep dressing. At the time of each dressing the response to the fistula test becomes less marked, until about 4 weeks postoperatively, when the fistula test gives a completely negative result. When regeneration of bone does not take place, the response to the fistula test continues to remain strongly positive, showing no signs of decreasing intensity. He believes that it is reasonable to assume that a fistula which has not shown signs of beginning regeneration of bone after 2 months will remain permanently open.

ACUTE OTITIS MEDIA

Of the 1324 infants less than 1 year old admitted to the Alder Hey Children's Hospital during 1936, G. McConkey and E. C. R. Couper¹⁶ found that 195 (14 per cent) suffered at one time or another from otitis media or otitis media and mastoiditis. In a certain proportion the otic infection was undoubtedly secondary to some other pathologic process. The remainder were cases in which the infection appeared to be responsible for the child's illness and in which, in the majority, suitable treatment of the ear resulted in improvement. The latter is called primary. Any doubtful case was included in the secondary group. In the secondary group (74 cases) associated with respiratory infections the greatest number of cases and the highest death rate (31 per cent) occurs in the age group from 3 to 9 months, while in the group (21) associated with nutritional disturbance the greatest number occurs in the age group from birth to 6 months,

with a death rate in this group of 45 per cent. In the group associated with nasopharyngitis (12 cases) the greatest mortality (33 per cent) was in the age group from birth to 6 months. In the 9 cases of otitis media complicated by another infection there were 4 fatalities. The previous method of feeding these children does not appear to influence the results. There were no deaths in the 7 cases of primary classic mastoiditis. In the 33 primary cases of otitis media and mastoiditis the death rate was 84.8 per cent and the highest death rate appears to be in the age group from 1 to 3 months. All of the 39 children with mild primary otitis media and mastoiditis recovered. Among the patients with classic mastoiditis only 1 was breast fed for more than 3 months, while the remainder all had shorter periods of breast feeding. Operation is always indicated in classic mastoiditis and the results are good, in the toxic group the results are poor and in the mild group the results are good in selected cases. Once the infant's infection so overwhelms it as to produce symptoms of toxicity, its chances of survival are just as great with conservative treatment as with surgical intervention. The analysis of the seasonal incidence of the primary group shows that the greatest numbers occur during the months of July, August, September and October, the season of the year when diarrhea and vomiting are most prevalent in infancy. Confirmation is afforded for the theory already advanced by numerous authors that the well-known diarrhea and vomiting syndrome is frequently caused by the presence of otitis media and latent mastoiditis, the pathology of which is of the nature of a retention phenomenon with lack of satisfactory drainage.

A study of the ear complications among 3564 scarlet fever patients is

presented by A. L. Hoyne and R. Spaeth.¹⁷ This number represented patients treated during the period of July 1, 1934, to June 30, 1935. There were 510 cases (14.3 per cent) which compared favorably with figures of 134,862 cases culled from the literature (11.8 per cent). The authors record the fact that 215 (45.16 per cent) of 476 cases of purulent otitis media developed mastoiditis. The incidence of this complication was significantly higher among the fatal than among the recovered cases of suppurative otitis media. A total of 124 cases (57.6 per cent) or 347 per cent of the total number of cases, required surgical treatment, the remainder were given solely medical therapy. There was a mortality of 14.51 per cent among the operative cases and 5.49 per cent in the nonoperative group. It is of interest to note that the majority of cases of otitis media occurred in the first week, over 70 per cent in the first 3 weeks.

W. Giese¹⁸ studied 27 cases of nephritis in patients with acute otitis media, which were observed at the otolaryngologic clinic of the University of Jena during the years from 1932 to 1937. These 27 cases of simultaneous nephritis and acute otitis media represent 2.45 per cent of the 1102 cases of acute otitis media which were treated during that period. Among the 403 cases of chronic otitis media, nephritis was never observed. The 27 cases of concurrent nephritis and acute otitis media are classified into 4 groups, which differ greatly as regards type and course of the disease. In the first group of 7 cases an acute nephritis developed in addition to an acute otitis media. The nephritis developed either several days or several weeks after the onset of the otitis media, usually following after a new attack of general infection, which was recognizable on the increase in temperature. Generally the

nephritis is independent of otitis media, but it may originate in the ear as the result of a surgical trauma by way of the blood stream. In the second group of 2 cases an acute nephritis became complicated by an acute otitis media. These cases were characterized by a severe disturbance in the general condition. The otitis media developed independently of the nephritis but, as a result of the inadequacy of the defense powers of the organism, the otitis media developed sooner than would be the case otherwise. In the third group, which comprised 16 cases, acute otitis media and acute nephritis developed simultaneously, frequently accompanied by diseases of other organs, particularly the rhinopharyngeal organs. The general condition is extremely poor. It cannot be determined from the outset and the course of the disease whether the nephritis is dependent on the otitis media. In the fourth group of 2 cases on acute otitis media developed in addition to a chronic nephritis. Observations revealed that the aural and renal diseases concurred and did not influence each other noticeably. Thus a real dependence of the nephritis on the otitis media cannot be detected in all cases and the author rejects the notion that acute otitis media is a focal infection. The concurrence of acute otitis media and nephritis as well as of other local diseases is the result of a general infection which is frequently of tonsillogenic or pharyngogenic origin. The concurrence of oral and renal disease makes no essential difference in the therapy. Surgical treatment is not necessarily more urgent or more frequent. Treatment of the ear exerts little influence on the severity or the course of the nephritis. The ear and the kidney should be treated in the usual manner and a thorough general therapy should be combined with the treatment of these organs.

V. Schmidt¹⁹ says that in acute inflammation of the middle ear treated by his method the functional results, without aftertreatment with the air douche, have been particularly good, the number of operations small, the mortality low and the average hospitalization not longer than with other conservative treatment. Early paracentesis is called for, after which hot compresses are applied for 24 hours. Syringing with 33 per cent by volume or 27 per cent by weight of alcohol at 37° C is then begun. A record syringe of from 10 to 20 cc. is used, with a rubber disc attached to the cone and held to the external ear. The fluid reaches the tympanum under a certain pressure by which the discharge on the tympanum is more readily removed with the fluid as it flows back to the disc. Individualization is necessary as to the frequency and number of treatments. In rare cases irrigation 3 or 4 times a day suffices, 6 times daily is the rule and more frequent daily flushings are given in cases of high temperature and a tendency of the paracentesis opening to close. Paracentesis was repeated in less than every tenth patient. The patients often notice alcohol in the rhinopharynx, which shows that the eustachian tube has become passable, favorably increasing the drainage of the middle ear, with simultaneous rapid improvement in hearing. Syringing with 27 per cent alcohol causes pain only when the treatment is delayed, so that the canal is raw. If there is pain from the mucous membrane of the middle ear, a 2 per cent solution of nupercaine is added for the first days. The author asserts that as far as he knows the combination of disinfection and astringent action with improved drainage of the middle ear through syringing with alcohol is not attained by any other agent. Of the 103 patients treated in 1936, 12 (11.7 per cent) were operated on; of

these, 8 had mastoiditis on admission. After re-examination in 1937 of 218 patients, most of whom had been observed for more than a year, showed that neither mastoiditis nor other complications had followed. In 210 cases the tympanum had healed, in 25 with small cicatrices, mostly linear; in 5 cases there were small, sharp-edged perforations, with normal hearing, in 1 a larger central perforation, in 2 a moist inner ear. Hearing was normal in 208 cases. In the complete material of 295 cases from the period of treatment with syringing with alcohol the mortality was about 1 per cent; 2 of the 3 patients who died were operated on immediately after admission.

In the course of a year all of Jorgensen's patients with otitis media were, if immediate operation was not indicated, treated by syringing with alcohol according to the Schmidt method, either 24 hours after paracentesis in recent otitis or from the day of admission in cases of spontaneous perforation or paracentesis done before admission.¹⁹ There were 357 patients, with 509 cases of acute suppurative otitis media. In 3 cases treatment had to be terminated because of unbearable pain in connection with the syringing, in most cases there was pain from 2 to 5 minutes after irrigation, especially during the first days, and a few patients felt no pain. In 247 cases, recovery resulted, in about two-thirds of these the treatment was begun 24 hours after the incision of the eardrum, in one-third at a later stage. Seventy-five patients (29.3 per cent) were operated on in spite of the treatment. The 410 patients with 584 cases of acute suppurative otitis media from the preceding year constitute the control material. Of these, 37.8 per cent were operated on. The author sees as drawbacks the need of hospitalization, the painfulness of the treatment and the long duration of the

treatment; the advantages are the reduced number of patients operated on, the infrequency of a second paracentesis, the absence of eczema in the middle ear and external ear and the possibility for direct effect on the middle ear and the eustachian tube.

J. H. Maxwell²⁰ points out that if a patient with otitis develops symptoms of sepsis, the sepsis is not necessarily due to the ear infection. The otitis may be "an incident in the course of an infection elsewhere responsible for the patient's sepsis." Therefore, since cases of otitic sepsis are rarely surgical emergencies, a careful study should be made to determine whether the sepsis is definitely of otitic origin.

Such a study includes bacteriological studies of the aural discharge. A record of the temperature, pulse, and respiration every 2 hours. Daily blood counts at the same hour; increasing leukocytosis, progressive secondary anemia and an increase in the number of immature polymorphonuclear leukocytes are significant. Daily examinations of the urine including the study of the stained sediment after centrifugation, as streptococci may appear in the urine before they can be demonstrated in blood cultures. Daily blood cultures, taken either at the peak of a temperature rise or right after a chill. Examination of the patient twice a day with special reference to the possibility of endocarditis, pneumonia, renal infection, acute exanthem, intracranial involvement and jugular phlebitis. X-ray examinations of the chest should be made every 24 to 48 hours, as the x-ray may show an acute pneumonitis before physical signs are definite. Radiographic examination of the mastoids is also important; a diploic structure is more frequently found when the ear is the source of the infection

Treatment—If it is definitely determined that the otitis is the cause of the sepsis, operation is indicated. The operative procedure should include careful *exenteration* of "all possible pneumatic bone"; on several occasions, the author has found apparently healthy bone on the floor of the mastoid concealed a small parasinal abscess. The *sigmoid sinus* should always be *exposed widely* in septic cases. If the sinus appears normal at the time of operation, but the symptoms of sepsis do not subside, a second operation is indicated for the ablation of the sigmoid. Prior to this second operation, however, it must be definitely established that the contralateral ear is not a source of infection; a complete mastoidectomy must sometimes be done on this ear. The sepsis does not subside immediately even if the active focus has been adequately removed. Postoperative treatment is important. This should include. Forced fluids to 4 to 5 liters a day for adults; high caloric, high vitamin diet, reduced iron (0.5 Gm 3 times daily); repeated small transfusions of blood from different donors. In hemolytic streptococcus infections sulfanilamide may be given, preferably by mouth.

CHRONIC OTITIS MEDIA

M. M. Cullom²¹ arrives at the following conclusions on the problem of chronic suppuration of the middle ear and mastoid after 16 years of investigation. (1) At least 85 per cent of purulent infection of the middle ear and mastoid are the result of a purulent sinusitis, nearly always on the same side as the infected ear and mastoid. (2) Of those having scarlet fever, 91 per cent have a coincident infection in the sinuses. It is presumed from clinical symptoms that about the same percentage have a coincident sinusitis in epidemic influenza.

(3) If 91 per cent of patients ill with scarlet fever and influenza, together with those having sinusitis in the other exanthematous diseases, have infection in the sinuses, at one time or another practically the entire population suffers from sinus disease. (4) A large proportion of those so infected are left with a chronic sinus infection that tends to last throughout life unless diagnosed and treated. (5) These chronic residual infections constitute a menace to the life, health and hearing of those so infected and make the victim a carrier infecting others by contact and starting epidemics. (6) What is diagnosed as an acute sinus infection is often an acute exacerbation of a chronic sinus infection. (7) When the relationship is established between a chronic middle ear suppuration and a purulent sinusitis, the first step in the treatment of the ear is the elimination of the sinus infection.

Treatment—Connell²² ceased the use of watery irrigation in the treatment of acute or chronic infections of the ear. The so-called dry treatment avoids many of the objections to watery solutions. The objection is not alone the soggy condition of the external canal but also the fact that many of these infections are kept active by the irrigative solution in the middle ear. The dry treatment is carried out by the use of *cotton wicks*. The wicks are changed as often as one-fourth of their length is wet. It may be necessary to change them every 10 or 15 minutes if the discharge is profuse. If it is felt that one must irrigate an acute or chronically infected ear, it is best to use 70 per cent alcohol. Most chronically infected ears will heal if kept clean.

Pratt in 1930 suggested what may be called "continuous drainage" by the use of cotton wicks. His method is to roll cotton on an applicator and clean the ear and then cotton in the form of a wick

is left in the canal a little distance from the tympanum and replaced as often as it is soiled. The cotton wick should be long enough to rest comfortably on the tympanum and to protrude far enough from the external canal to be removed easily. It should not be large enough to fill completely the canal, as that would tend to make a soggy condition of the membrane and canal, which would be inimical to healing and could possibly cause furunculosis. About 6 years ago the author began the use of vitamins in the treatment of all chronically infected ears. Halibut or cod-liver oil, to the equivalent of 3 or more teaspoonfuls of standard *cod-liver oil*, and from 3 or 6 *brewers' yeast tablets* a day with the addition of *orange* or *lemon juice* to the diet have been used. The results have been satisfactory. With the wicks, which by capillary attraction are a form of continuous drainage, and the vitamins, infected ears have healed and a secondary membrane has formed when all other conservative means of treatment have failed.

P. S. Martins, Jr.,²³ has never found that urea harms the delicate epithelium of a radical mastoidectomy cavity and he has used it on exposed dura without signs of irritation or toxicity. Occasionally on acutely inflamed or raw tissue there is some pain, but this is seldom comparable with that produced by alcoholic solutions. He also observed its effect on a number of patients with chronic disease of the ear and was more than pleased with the results. Patients who underwent radical mastoidectomy have been treated in a similar manner, with equally pleasing results. It has almost eliminated the necessity of daily packing, punching and scraping. The treatment has also been tried on several patients who came in for cleaning of radical mastoidectomy cavities and it was

found that a week's use of a solution of urea cleaned out almost all débris, leaving the skin pink and healthy. In chronically infected middle ears in which the saturated solution could be brought in contact with the diseased area satisfactory results, with few exceptions, have been obtained. Eleven other persons with chronic otitis media with large perforations were treated by dropping a saturated solution of urea in the ear twice daily. The odor was rapidly eradicated and all the ears are dry and clean at the time of writing. One had been treated several times by ionization without success, and many had had several different courses of treatment, with only temporary relief at best.

To avoid complicating the results the author has used *urea* alone satisfactorily, although he sees no reason why it should not be combined with any form of therapy which the individual physician might favor or the variation of the condition warrant, with even greater success. Indeed, the work of Holder and McKay on various combinations of urea with other forms of therapy is of interest and will undoubtedly be of value in selected cases of aural disease. The solution is applied with a dropper twice daily, beginning with small amounts and increasing rapidly if there is no pain. The crystals may be applied directly or with a powder blower, care being taken to remedy any caking either in the canal or in the powder blower. A small amount of water or saline solution will usually correct this. In a few cases there will be some pain at first. Neighboring pathologic processes or factors in the general health of the patient, which often assume a dominating rôle in prolonging infection, anywhere, should not be overlooked, for urea therapy is not a cure-all or a new magic healing power, the results being due simply to a more adequate removal

of the gross and microscopic débris in the recesses of the middle ear, giving nature a fair chance, often with surprisingly successful results.

LATERAL SINUS PHLEBITIS

The extent of brain injury with the localization of the thrombi in the venous sinuses and their tributary veins in 80 cases of thrombosis of the dural venous sinuses in children, all but 3 of whom were less than 3 years of age, were correlated by O. T. Bailey and G. M. Hass.²⁴ Especial attention is given to the large group of infants and children in whom the thrombosis could not be attributed to the localization of a demonstrable infectious agent in the sinus wall or tributary veins. Forty-two cases were associated with various forms of sepsis: meningitis, scalp infections, otitis media, mastoiditis and bacteremias without meningeal localization. Four instances followed surgical procedures. Thirty-three patients presented no evidence of infection of the central nervous system or blood stream. They were all infants less than 30 months of age. The illness began with an acute nutritional disturbance usually followed after a period of days or weeks by evidences of meningeal irritation, marked hyperpyrexia and convulsions or other abnormal neurologic manifestations. Some infants died without any evidence of neurologic disturbance. In all these patients the superior longitudinal sinus was thrombosed in its entirety or in part with variable involvement of other sinuses and cerebral veins. Twenty-one of the patients presented hemorrhages into the meninges associated in 19 cases with intracerebral hemorrhage and necrosis. Some of the patients succumbed within a few hours after the onset of the symptoms referable to involvement of the central nervous

system. A few lived for 10 days to 1 month. Finally 2 patients recovered from their acute attacks and died later with organized and canalized thrombi in their superior longitudinal sinuses.

Plethysmometry of the nose and the patency of the sigmoid sinus and jugular vein were described by van Dishoeck,²⁵ directing attention to the fact that in case of obstruction of 1 jugular vein by means of unilateral compression of the neck, the inferior concha of the same side of the nose becomes swollen, because the venous blood coming from the endocranium causes a congestion of the pterygoid plexus. In some cases this swelling can be detected by anterior rhinoscopy, but by means of an especially constructed nasal plethysmometer the swelling can be detected in nearly all those cases. The author describes and illustrates this nasal plethysmometer. He shows that, because the swelling can be detected in nearly all cases, it can be utilized as a symptom of obstruction of the jugular vein and of the sigmoid sinus in cases of thrombosis, of pressure by brain tumor or brain abscess and of congenital absence of the sinus or jugular vein. In this case the symptom will be negative on the side of the obliteration and strongly positive on the other side.

C. W. Irish²⁶ studied 1000 cases of cerebral vascular lesions found in 12,500 consecutive necropsies done at Los Angeles General Hospital. Of this number, 133 were found to harbor cerebral embolic lesions, 418 hemorrhagic processes and 449 thrombotic pathologic conditions, among which 98 (9.8 per cent) were sinus and venous thromboses. These 98 cases of cerebral venous system involvement have been reviewed with an exposition of the comparative incidence of the various types of lesions, of the contributory factors and etiologic sources in their production and of the sex, age

and survival periods in the patients demonstrating these intracranial pathologic changes. Lateral sinus thrombus was found present in 38 cases, the sinus on the left being involved in 25, on the right side in 10 and bilaterally in 3. The longitudinal sinus was involved in 16 cases and the cavernous and its accessory sinuses in 34; venous thromboses were disclosed in 10. The history of the development of knowledge regarding these conditions is reviewed with particular attention to diagnostic procedures, the sources and pathways of infection and the opinions regarding the surgical treatment. Bacteriologically the streptococcus is the causative agent of sinus thrombosis in 60 per cent of the cases, according to Seydell. *Streptococcus mucosus* is especially virulent and characterized by late exacerbations with fatal outcome. In chronic cases anaerobes and facultative anaerobes may be the causative organisms. In the majority of sinus thromboses the infection is from 1 organism.

The differential diagnosis between sinus phlebitis and all other conditions wherein septic temperature and chills may be present is often attended by great difficulties.

Certain diagnostic features which aided in making the correct differential diagnosis between thrombosis of the lateral sinus and acute bacterial endocarditis have been stressed by H. Rosenwasser.²⁷ When the Ottenberg differential blood culture indicates large number of colonies in the cultures of blood from the jugular vein and a peripheral vein in the arm, it points to endocarditis as the cause, whereas a large number of colonies in 1 or both jugular veins and many fewer colonies in the arm point to sinus thrombosis. Correlation of the bacteriologic characteristics of the aural discharge and the pus from the mastoid with blood cultures, as described by

Libman and Celler, Ottenberg and Friesner, is helpful. Important in the differential diagnosis is the fact that none of the pneumococci with the exception of the type III pneumococcus cause sinus thrombosis. The significance of the embolic phenomena should be emphasized again because of their diagnostic importance. Cutaneous embolic lesions, petechiae, have never been observed by the author in a case of sinus thrombosis uncomplicated by bacterial endocarditis. Changes of the fundi, varying from slight blurring of the margins of the discs to 4 diopters of papilledema, occurred in 16 per cent of the cases of sinus thrombosis which Rosenwasser and associates observed. It is uncommon in a case of acute endocarditis to note any change in the fundi other than embolic lesions or their manifestations, namely, petechiae, Roth spots or Doherty-Trubeck lesions. The changing character of the cardiac murmur or murmurs from day to day is significant of endocardial involvement. A definite history of aural disease, mastoiditis and a tender gland at the angle of the jaw associated with corroborative local evidences of venous involvement are additional factors in determining the correct diagnosis. In conclusion, it must be apparent that these cases of serious borderline conditions require the closest co-operation between the otologist, the internist and the bacteriologist for their proper solution.

Treatment—From a comprehensive review of the literature based on the anatomic, physiologic and pathologic conditions involved in the causation, production, and distribution of suspected thrombosis of otitic origin and from the study of the records of past clinical experiences, it appeared to J. M. Sutherland²⁸ that no unified surgical procedure can be adapted for this condition other than the eradication and drainage of the

primarily infected area. The author feels that the use of surgical intervention on the jugular vein is still controversial. While great advances have been made in the diagnosis and treatment of sinus thrombosis, much still remains to be desired in treatment in accomplishing a complete eradication of infected foci.

The salient features of 21 consecutive cases of otitic sepsis were discussed by A. J. Juers²⁹. In his series a definite chill preceded the elevation of temperature in all adults but was absent in patients below 10 years of age. One-third of the patients between 10 and 15 years had chills. Blood cultures were positive in 11 cases and there were a few instances where leukocytosis was absent. While the series is too small to warrant any definite conclusions as to the value of ligation of the internal jugular vein in the treatment of otic sepsis, the author feels that the procedure seemed to be the least essential in the management of the condition. Juers reports a mortality of 24 per cent.

The treatment of lateral sinus infections without operation on the jugular vein is presented by E. M. Atkinson³⁰ in reporting a series of 15 cases. Thrombosis of the sinus was present in 5 cases. Operation on the jugular vein was necessary in only 2, in the 1 only because the condition had been allowed to progress too far before operation and in the other because of repeated rigors from a disintegrating clot in the jugular bulb. Necrosis of the sinus wall without thrombosis but with infection of the blood stream and positive blood culture was found in 2 cases. Atkinson feels that ligation of the jugular vein need not be an invariable accompaniment of an operation on the lateral sinus; that it has its most valuable application when thrombosis has extended to the jugular bulb and, finally, that infection of the lateral sinus has a

marked tendency toward spontaneous cure if infected tissue is removed and free drainage provided.

VERTIGO

Vertigo as a symptom has always been of interest to physicians generally. The reasons are especially obvious to those who have made efforts to treat the condition in some individuals. Several types of vertigo are recognized, but most of them are based on some systemic etiology. Aural vertigo, however, is quite another matter. It is a well-established clinical state, which, together with other classical symptoms, comprise what is commonly known in otologic circles as Ménière's disease.

The cause of this unfortunate malady is not known. In some cases the attacks may be precipitated by a sudden movement, but generally there is no known inciting factor. Gardner recently remarked that, while in the mild cases the disease is very disconcerting, in the severe forms, though not dangerous to life, it is almost as disabling as is epilepsy to which it was likened by some of the earlier writers.

The *medical treatment* of Ménière's disease has been of little or no benefit to afflicted individuals even in the milder states. The *Furstenberg salt-free diet*, while helpful in some cases, has not proved curative, and, furthermore, recurrent paroxysms have been experienced in a number of instances after cessation of the diet even following prolonged periods. It is because of failure with medical therapy that neurologic surgeons have attempted to demonstrate the feasibility of relieving this syndrome by *intracranial division of the eighth nerve*. It has been pointed out that this procedure is called for only when the symptoms are severe and that it is not

justifiable when a patient is too enfeebled to undergo an operation which to one in ordinary health entails very little risk.

S. J. Crowe³¹ studied 117 patients seen at the Johns Hopkins Hospital during the last 9 years. In 23 the disease was relatively mild and no immediate operation was indicated; they have been re-examined from time to time. In 94 patients the attacks were disabling and they came to the hospital to have their vestibular nerve divided. The author believes that stimulation of the vestibular end organs is the cause of the sudden, violent attacks of vertigo, the sensation of surrounding objects whirling and the temporary staggering gait in Ménière's disease. When the central vestibular pathways are irritated by a new growth, the dizziness and in-co-ordination are constant, there is no sensation of objects spinning in a rotary direction, and the periods of freedom from all vestibular symptoms so characteristic of Ménière's disease is a form of aural vertigo that involves the cochlea as well as the static labyrinth. Ménière's disease is a combination of vestibular and auditory disorders. The diagnosis is made largely on the description of the attacks of vertigo. Too much emphasis placed on special examinations (the audiometer, tuning fork and vestibular tests) may lead to confusion. Of the 117 patients, 74 were men and 43 women. Only 10 of 71 patients had a history of otitis media at any time, and only 2 had an infection of the accessory nasal sinuses when admitted to the hospital. Vertigo, the symptoms that disables these patients, is always cured by an intracranial division of the vestibular nerve. The deafness and tinnitus are only slightly less disturbing.

In a clinical study, A. J. Wright³² discusses 73 cases of vertigo from sup-

puration of the middle ear. The disease does not result from a lesion in the middle ear but is primarily in the labyrinth. It is marked by an increased irritability of the labyrinth, as shown in the cochlea by hyperacusis and in the vestibule by an abnormal reaction to normal stimuli, such as movements of the head or to minimal abnormal stimuli, such as some alteration of tension in the middle ear. Focal infection is invariably present, and frequently other lesions exist, especially chronic iritis. All patients with *aural vertigo* treated by **eradication of a septic focus** or foci are now completely free from vertigo. The author believes that cases of labyrinthine vertigo, which have been regarded as of unknown or doubtful etiology, can be grouped together as belonging to a single disease which he calls "focal labyrinthitis." This disease is an inflammation of the labyrinth. He bases this view on the occurrence of nerve irritation, both auditory and vestibular, signs of tension and progressive loss of function, and on the signs of tension and progressive loss of function, and on the analogy with a known inflammatory lesion, chronic iritis. It is not, in his opinion, the result of disease in the middle ear. That it is secondary to a focus of infection is shown by the invariable presence of such a focus and, to a greater degree, by the arrest or even cure of the disease when such a focus is eradicated. This he believes is the only hypothesis that explains the many isolated observations in the literature which do not fit into the present somewhat indefinite ideas of its pathology.

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DISEASES OF THE PHARYNX

By A. R. HOLLENDER, M.D.

TONSILS

Anesthesia—In an effort to discover a substance which would produce beneficial prolonged anesthesia for tonsillectomy, A. F. Laszlo and R. F. Hauck¹ experimented with various preparations. While 1 or 2 of them proved effective, they had to be abandoned because of the high degree of toxicity and the varying susceptibility to them.

Eucupin dihydrochloride with 1 per cent procaine hydrochloride has been shown to give satisfactory prolonged anesthesia in proctology. It was used by the authors in tonsil work in over 300 cases without any evidence of sensitivity. Since solutions stronger than 0.2 per cent may cause local reactions, higher concentrations should not be used. The prolonged anesthetic action of eucupin is explained on the basis of slow diffusibility in the tissues. Because of the slow absorption and consequently delayed initial action, procaine hydrochloride 1 per cent was added to the solution.

Anesthesia with the combined solutions has been adequate and there was experienced postoperative freedom from pain from 5 to 48 hours. No toxic symptoms have been encountered and healing has not been delayed.

In the opinion of the authors, eucupin-procaine solution has proved itself superior both in anesthetic efficiency and in the prolongation of analgesia to any other local anesthetic in their experience.

Tonsillectomy and Arthritis—The influence of tonsillectomy on the course of rheumatic fever and rheumatic heart disease was studied by W. B. Allan and J. W. Baylor². One hundred and eight patients comprised the series, 90 having been followed from 10 to 23 years and

18 from 1 to 10 years. The follow-up period of 16 of the latter group was terminated by the death of the patients. The average age of the 86 living patients was 26.4 in 1935. The 11 patients followed for from 1 to 5 years had recrudescences, 3 single and 8 multiple. All the patients in this group died from rheumatic cardiac disease. Fifteen patients were followed for from 6 to 10 years; 8 had recrudescences, 4 single and 4 multiple. Five of these patients died; 2 deaths were due to rheumatic cardiac disease, 1 to tuberculosis, 1 to erysipelas and 1 to peritonitis following an appendectomy. Twelve of the 36 patients followed for from 11 to 15 years had recrudescences, 3 single and 9 multiple. There were 2 deaths in this group, 1 from rheumatic cardiac disease and 1 from nephritis. Thirty patients were followed for from 16 to 20 years and of these, 12 had recrudescences, 4 single and 8 multiple. There were 3 deaths in this group, 2 from cardiac disease and 1 from drowning. Of the 16 patients followed for from 21 to 23 years, 4 had recrudescences, 2 single and 2 multiple. The single death in this group was due to acute rheumatic fever with pancarditis.

Since rheumatic cardiac disease developed in only 6 of the 49 rheumatic patients not having cardiac involvement at the time of operation it is concluded that tonsillectomy and adenoidectomy are to be recommended in the treatment of rheumatic fever. The incidence of persistent infection of the nasopharynx was considerably higher in the patients who had recrudescences than in the entire group. Recrudescences were common in the first 5 years after operation. Most of the patients who had repeated recru-

descences during this period died of rheumatic cardiac disease. Rheumatic cardiac disease occurred more frequently in patients having recrudescences, and deaths from rheumatic cardiac disease occurred only in this group.

PARAPHARYNGEAL ABSCESS

Hemorrhage—Parapharyngeal hemorrhage was considered by F. W. White and L. Hubert,³ who presented 6 case histories of 4 males and 2 females. The youngest patient of the series was 5½ years, and the eldest, 60 years. Concomitant conditions especially were scarlet fever, diabetes mellitus, 1 tooth infection and extraction. Four required operative procedures, and 2 recovered under conservative treatment.

Special stress is laid upon the relationships and contiguity of the ninth, tenth and twelfth cranial nerves, the cervical sympathetic trunk and its superior ganglion, the means of communication between the parotid space and the pharyngomaxillary space by means of a gap in the fascia, and also the presence of the facial nerve in the parotid space.

An analysis of the case reports of parapharyngeal infection submitted suggests the following:

- 1 The degree of infectivity of the causative organism for a given person determines the seriousness of the parapharyngeal invasion.

- 2 Conservative treatment of parapharyngeal infection is in many instances successful.

- 3 Free, active hemorrhage from the throat, with or without apparent throat inflammation, requires not local treatment, but bold, external operative measures.

- 4 Meddlesome incision of a lateral pharyngeal swelling may lead to hemorrhage. If left alone, and treated conservatively, ligation may not be necessary.

- 5 Aural hemorrhage, associated with parapharyngeal infection, requires immediate ligation of the common carotid artery.

- 6 If any doubt exists regarding erosion of the internal carotid artery, the external carotid

and the ascending pharyngeal arteries should be ligated, and a loose ligature placed around the common carotid artery.

7. Ligation of the common carotid artery, when done slowly—minutes, not seconds—and an attempt is made to actually prevent the flow of blood beyond the ligature, not necessarily to feel the severance of the intima, is a life-saving operation, as compared to temporizing methods by the intrapharyngeal route.

8. Throat and ear hemorrhages associated with trismus, involvement of nerves, as noted above, lateral pharyngeal tumefaction, sepsis, swelling and tenderness of the corresponding side of the neck, indicate pharyngomaxillary fossa infection.

Treatment — Early and thorough *drainage of deep infections of the neck* seems to be the message of those who have studied the subject more than just casually. H. B. Orton⁴ emphasizes that delay in instituting early and courageous treatment in deep infections of the neck, particularly in the lower half, may prove disastrous. An accurate history to enable one to visualize point of entry of possible infection and the anatomical planes which the infection may follow are essential. L. C. Boemer,⁵ after a survey of 75 cases, found that involvement of the pharyngomaxillary or parapharyngeal space and the great vessels of the neck constituted the greatest hazard to life. Fatality from unrecognized deep pus in the neck secondary to tonsillitis and peritonsillar abscess still occurs. Early adequate drainage of the parapharyngeal space must be obtained and this is best achieved externally.

MOUTH INFECTIONS

The value of *zinc peroxide* in mouth infections was investigated by J. P. Wintrup.⁶ This worker used this preparation in treating cases of acute Vincent's infection, 8 cases of chronic Vincent's infection, 12 cases of acute gingivitis, 3

cases of suppurating periodontoclasia and 2 cases of radiation necrosis

Zinc peroxide is quite stable and comes not as a pure salt but contains from 45 to 50 per cent of zinc carbonate. Only the "medicinal grade" should be used and it must be heated to 284° F. (140° C.) in quantities of not more than 1 lb. (500 Gm.) for 4 hours, to effect sterilization, in accordance with the manufacturer's specifications. Zinc peroxide with 7.5 per cent of available oxygen, nearly as much as sodium perborate, loses its oxygen slowly. Therein lies its great virtue for the treatment of oral infections. Zinc peroxide has a pH of 8.8 and remains stable over a long period, giving up its oxygen so slowly that great amounts of it can be utilized to permeate interstices, crypts and pockets, in which organisms associated with all types of gingivitis, pyorrhea, osteomyelitis and necrosis of the soft tissues abound. Further, the zinc oxide residue is bland and healing and thus is an added desirable characteristic.

Best results are obtained when the zinc peroxide is applied as a paste. Following application of local medication, zinc peroxide is used by the patient at home every 3 hours for the first 24 to 48 hours and then every 4 hours. It is recommended that the zinc compound be mixed with water to form a creamy paste. One-half teaspoonful for each application is sufficient. This paste is applied by the patient with his finger or on a sterile swab and massaged gently into the interproximal spaces between the teeth and along the gingival margin. The zinc peroxide thus is placed directly in contact with the tissues and remains there for a long time, giving off its oxygen. No effort should be made to rinse the mouth and, as the powder is slowly mixed with the saliva, the patient should expectorate this residue. Patients are seen every other day for further local treatment;

the zinc peroxide is continued until complete healing has taken place, and then for another week as an added precaution.

Vincent's Infection

The therapy of fusospirochetosis is discussed by T. B. Wood,⁷ who endeavors to iron out some of the lack of understanding of this important subject. He contends that the usual therapy in vogue today is not curative, that *sodium oleate solution* therapy is. On the administration of sodium oleate solution, according to the author it is important, first, to use it frequently enough, from 15-minute to 1-hour intervals, to discourage new colonies from forming from the remaining spores between applications, second, to use it in small quantities, ½ to 1 ounce, at one time, so as not to dry the mucosa excessively, third, to use it in as hot a solution as can comfortably be tolerated because its antiseptic power is increased directly with the temperature.

It is essential to explain to the patient that this solution of 1 ounce is to be thoroughly introduced into the pus pockets between the teeth and gums every time the mouth is rinsed or the throat gagged. To use larger amounts is of no value and is drying to the mucosa. Agitation is important.

All forms of treatment, whether general or local, all analgesics, barbiturates and derivatives, astringents, antiseptics, antipyretics and neosalvarsan or brands of sodium perborate must absolutely be cut out. *Vitamins, endocrines, insulin* and so on may be used to take care of the deficiencies. Although these substances have no direct action against the specific infection they certainly help the well-being of the patient. Vitamin B complex, as well as ascorbic acid or vitamin C, and vitamin A are especially useful.

Another point to remember is that allergy is rather rare yet may be encountered, but no damage can result as the cure takes effect as rapidly as the allergy. There will certainly be no granulopenia, as is likely to result fatally from the use of some of these other drugs.

The only chance of failure is when proper instructions are not given the patient or the patient does not follow the proper instructions intelligently. The solution must come in contact with the organism.

STREPTOCOCCIC PHARYNGITIS

The widespread utilization of *sulfanilamide* had led to its trial in beta-hemolytic streptococcus pharyngitis by J. R. Gallagher.⁸ Observations were made on the value of the new drug in 33 cases of pharyngitis caused by strains of beta-hemolytic streptococcus of low virulence for mice. The administration of doses of sulfanilamide in amounts equivalent to 1 Gm of sulfanilamide per 10 kg of body weight daily early in the course of these cases of pharyngitis apparently shortened the length of time during which throat cultures continued to be positive for those bacteria in a significant proportion of cases. The results obtained in this study suggest that small doses of sulfanilamide given early in such an illness are usually without demonstrable effect. When small or large doses are given late, it is impossible to be certain that subsequent throat cultures have become negative because of the specific therapy. The use of sulfanilamide in adequate dosage frequently produced mild toxic symptoms, such as headache, cyanosis and a morbilliform dermatitis; none of these manifestations were followed by serious consequences.

GRANULOCYTOPENIA

C. M. Marberg and H. O. Wiles⁹ report their results with *yellow bone marrow extract* in granulocytopenia. While one is reluctant to add another drug to the many now advocated, the encouraging results in 20 patients treated by the authors makes the present recommendation worthy of a trial when the opportunity offers. In all but 7 there was a rise in the number of granulocytes, usually with a return to normal figures. In fact, these writers claim that if active infection persists during the period of treatment the granulocytes may rise to figures far above normal. The rise in granulocytes usually begins within 24 to 36 hours, as contrasted with the effect of pentnucleotide, which is not usually manifest in less than 4 to 5 days. The product now employed is a concentrate prepared by extracting the unsaponifiable portion of the marrow and dissolving it in a bland oil for oral administration. The equivalent concentration of 2 Gm of marrow per drop has been found quite satisfactory for chemical use.

The failure of blood transfusions as a therapeutic aid in agranulocytosis has been unexplainable. It has, however, made the report of F. Lamer¹⁰ of special interest, since it modifies the transfusion in such a manner that one can be fairly optimistic of favorable effects. Because the normal human reaction to most infections is an increase in granulocytes, ascribable to certain reactions and changes, it should be possible according to Lamer, to supply this deficiency by transfusing blood from a donor in whom this principle has been activated by infection.

Accordingly, professional donors are treated with preliminary injections of milk and transfusions given during the

period of leukocytosis thus produced. Four cases of agranulocytosis are reported representing 2 forms of the disease. In the first 2 which revealed on blood examination 400 to 500 leukocytes, 6 transfusions of "fever blood" were administered at intervals of 2 to 3 days. From 6 to 12 hours after the first transfusion, the leukocytes increased to 3000; after the sixth transfusion the counts were respectively 6000 and 11,000 with definite shift to the left. Follow-up examinations 3 and 6 months later revealed normal blood and bone-marrow findings.

The remaining 2 cases, in which the etiology was industrial benzol poisoning, had leukocyte counts of 1000. Anemia was marked. One of the patients had a severe hemorrhagic diathesis; his general condition was poor. The damage to the bone marrow was evidenced by reduction of the entire cell count but especially of the myeloid cells. Both of these patients were dismissed with normal blood and marrow findings after 3 transfusions. Even though the series is small, the uniform results are dramatic with what might easily be labeled a simple procedure. The term "fever blood" may not be appropriate, yet it conveys the fact that the blood employed for transfusion is not that of the usual donor.

CANCER OF THE PHARYNX

According to H. E. Martin¹¹ the results of treatment of pharyngeal cancer have greatly improved since the introduction of *protracted*, or *fractionated*, *roentgen irradiation*, as developed by Coutard. The favorite results obtained in a certain percentage of cases have led to some overenthusiasm for this method and to attempts at the cure of all forms of pharyngeal cancer by protracted irradiation alone. The exclusive use of

roentgen radiation in all cases is probably not the best solution of the problem of pharyngeal cancer. Interstitial irradiation with radon may be used to great advantage in combination with protracted roentgen irradiation in many cases.

A combination of the 2 methods is of particular value for the treatment of an especially resistant portion of the primary lesion, a cervical node or such cervical metastases as may not advantageously be included within the skin portal except by the use of excessively large fields. The open mouths may be utilized as an additional portal for the treatment of many intraoral lesions and the lesions of the upper part of the pharynx. Undue effects on the skin and heavy irradiation through the salivary glands and the mandible are thereby avoided.

To obtain the best results in the treatment of the pharyngeal cancer, Martin holds that one must undoubtedly depend mainly on protracted roentgen irradiation, but the highest degree of success depends on the proper combination of methods and the supplementary use of interstitial irradiation with radon in a considerable percentage of cases. Entirely satisfactory and informative reports on end results must give specific figures for each anatomic form of cancer of the nasopharynx, and of the extrinsic part of the larynx.

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RHINOLOGY

By O. E. VAN ALYEA, M.D.

THE COMMON COLD

Etiological Factors—Chilling of the body surfaces is rapidly being accepted as the principle etiologic factor in acute infections of the upper respiratory tract. H. Marshall Taylor and Lucien Y. Dyrenforth¹ along with others make the statement that the human organism must maintain a constant average temperature of 98.6° F. (37° C), for any considerable degree of deviation will result in morbid changes. The extent of these changes was determined by a series of experiments carried out by Taylor and Dyrenforth. It was shown by their study that chilling unassociated with compensatory muscular activity leads to (a) peripheral vasoconstriction with attendant stasis and anoxemia, (b) lowered leukocyte response, both total and polymorphonuclear, and (c) impairment of the phagocytic capabilities of the fixed tissue cells including the nasal mucous membranes. They determined that one of the immediate results of these changes was a predisposition to infections of the upper respiratory tract, the paranasal sinuses, the eustachian tubes and the middle ear. E. C. Sewall, discussing the above paper, says that one must always distinguish between normal persons and those who harbor chronic infections in their sinuses. He thinks that ordinarily chilling induces infection in the latter group only and that normal individuals are but little adversely affected by a reasonable degree of chilling.

General Management—Bock² discusses the care of 1667 cases of acute infection of the respiratory tract treated by himself and his associates from September 1935 to March 1938. The subjects were undergraduate and graduate students at Harvard, the principal age range being from 17 to 25 years. The main purpose of his discussion is to make a plea for simple treatment, the fruits of which are best indicated perhaps by the relatively small list of complications (29 cases of otitis media, 1 of mastoiditis, 2 surgically drained antrums, 1 peritonsillar abscess and 52 of pneumonia) of all sorts occurring in this series. Common sense treatment of acute infections of the upper part of the respiratory tract, including the common cold, with or without fever, requires bed care. Whatever the specific etiologic factors may be, it is clear to the author that fatigue of body and mind in adult patients is a factor in the precipitation of these infections not generally recognized. The main principle of treatment should be *rest*. Energetic local treatment produces irritation of the nasopharyngeal membranes, often prolonging the course. *Salicylates* and *codeine* are used for comfort. Laxatives are not usually prescribed. **Control of temperature, humidity and dust** would add greatly to the effectiveness of treatment. Prevention of infections of the upper part of the respiratory tract by vaccines has little to support it. Lacking specific

means of therapy, the greatest advance on the problem at the moment would be made if the physician taught himself and his patients how to live within his and their physical resources, and especially within those of one's central nervous system. Such influences as chilling of the body, weather changes, irritative substances in the atmosphere and contagion must be taken into account; but granting these, under ordinary circumstances, the part played by the tension of living must be recognized more generally in solving the problem.

In the early stages of the acute head cold local treatment is usually not efficacious and can be actually harmful according to Lyle S. Powell.³ The congestion of the tissues of the upper respiratory tract is purposeful as is the increased leukocyte count and the elevated temperature.

Vaccine Therapy—Powell approves of a strong vaccine for the prevention and treatment of colds. He prefers intradermal to the subcutaneous injection and thinks in this manner he obtains less local but greater systemic reaction due to the slow absorption of the vaccine.

Immunization—An extensive study of the immunological action of *cold vaccines* was made by H. S. Diehle and coworkers.⁴ The study was carried out over a period of 3 years on a group of cold-susceptible students of the University of Minnesota.

A "control group" was observed during each year of the study. Such groups were chosen at random from the students who applied for cold prevention treatment, the members were treated in exactly the same manner as those of the vaccinated group, and they believed throughout the period of the experiment that they were receiving vaccine. Sterile physiologic solution of sodium chloride was administered hypodermically as a

control for the subcutaneously administered vaccine and lactose filled capsules as a control for the vaccines administered orally.

The group which received vaccine subcutaneously experienced an average of 25 per cent less colds per person than did the control group. This difference occurred during each year of the study and is statistically significant.

The group which received the polyvalent vaccine administered orally experienced just as many colds as the control group during each year of the study.

The results reported by the students who took Rosenow's streptococcus vaccine parallel exactly those reported for the control group.

Treatment—Oxygen metabolism is the central problem in medicine rather than infection is the belief of Jarvis⁵ who follows out this line of thought in the treatment of the early stages of a cold. His therapeutic list includes *insulin* in 3-unit doses which he gives daily to patients over 50 years old, for those between 20 and 50, he prescribes 5 to 10 minims of *dilute hydrochloric acid* per day while children are given small doses of *iodine (Amend's sol.)* 1 to 3 drops. These, he states, along with a *low carbohydrate diet* are very effective in preventing and terminating upper respiratory infections.

Nasal Suppuration in Infancy

Blotta⁶, stresses the value of *vaccines* and *specific serums* in the treatment of infants. *Antistreptococcic serum* is used locally in cases of nasal and sinus infection following scarlet fever.

INTRANASAL MEDICATION

Investigators again this year are stressing the dangers associated with the indiscriminate use of oily drops and

other harmful solutions in the nose. Recently Walsh and Cannon⁷, reported that oil, when given in large total amounts and over a long period, in this manner, to normal rabbits free from upper respiratory infections, seemed to initiate lesions in the lungs which could be demonstrated in roentgenograms. Edema, desquamative alveolitis and focal lipoid pneumonia were produced. As pointed out by these investigators, nasal oils when used clinically or employed because of rhinitis or upper respiratory disease, in passing through infected areas are likely to carry live organisms to the lungs. The combined effect of these factors, therefore, is serious. They instilled medicated oil into a normal rabbit, followed 24 hours later by a suspension of live microorganisms cultured from a rabbit with snuffles, granulomatous lesions were discovered throughout both lungs 20 days after the treatment. These granulomatous lesions contained oil. Intranasal administration of watery solutions of such commonly used medicaments as neosilvol, mild silver protenate, tannic acid, zinc sulfate and sodium sulfate, they found, resulted in pulmonary lesions including edema, necrosis and desquamation of macrophages. Such lesions were particularly frequent when antiseptics were given intranasally to rabbits with snuffles or when given mixed with living microorganisms. They also found that isotonic saline solutions containing such vasoconstrictors as ephedrine and neosynephrin did not cause pulmonary damage after intranasal instillation in normal rabbits. This work and the reports of others point to the potential dangers of intranasal medication and to the tentative conclusion that the only completely safe intranasal medicaments are weak saline solutions of appropriate vasoconstrictors. The use of nose drops containing antiseptics, as-

tringents or oily solutions may be, therefore, of doubtful advisability because of manifest irritating effects on the lungs.

Benzedrine as an inhalant has been found by E. M. Boyd⁸ to relieve nasal congestion but to have no effect on the duration of the cold. Experiments on frogs' ciliated mucosa using various vasoconstrictors were carried out.

In concentration of 0.05 and 0.1 per cent in distilled water, the following sympathomimetic compounds were found depressant towards ciliary movements of the esophageal mucosa of frogs and in the following order of decreasing toxicity benzedrin, benzedrin sulfate, ephedrin hydrochloride and meta-synephrine or neosynephrin hydrochloride.

EPISTAXIS

Etiology—Local causes of epistaxis are, according to J. P. Riggs⁹, (1) injury (a blow, sneezing, etc.); (2) ulceration, (3) new growth (adenoids, polyps, etc.), (4) varicosity of the veins of the nasal mucosa, (5) acute infective inflammation. General causes are high arterial or venous blood pressure, altered condition of the blood (as in anemia and the onset of acute specific fevers), and alternations in atmospheric pressure. There is also epistaxis of obscure origin, often attributed to congestion, occurring in childhood at puberty, and in women at the menopause.

Location of Bleeding—Bleeding is sometimes from both nares, but usually unilateral. Epistaxis may occur without anterior bleeding. If the patient is lying down, the blood may pass through the posterior nares and enter the nasopharynx.

If bleeding comes from a particular place, it will slow up or temporarily stop when cotton soaked with adrenalin is applied. This procedure will show

whether or not it comes from Kiesselbach's area. If the site is near the attachment of the middle turbinate, a small pad of cotton placed there will usually control it. This is a frequent site in arteriosclerotic cases.

One cannot localize bleeding in every case, and hemorrhage may be so profuse as to forbid too much intranasal observation. Then we must pack the nose, or do anything for immediate control.

Treatment—Posterior sponge packing is done in postoperative cases, and in those where there is continued hemorrhage down the pharynx, when anterior packing has failed. A soft rubber catheter is passed through the nose on the bleeding side, the end grasped by curved artery clamps in the pharynx and brought out through the mouth. A string is now tied to this end with a sponge, 3 inches long by 1½ inches thick, attached. The catheter is withdrawn through the nose and the sponge guided into position by the forefinger. This packing is left in position about 12 hours, occasionally longer, but the possibility of middle ear infection must be constantly kept in mind.

Submucous Elevation—Submucous elevation has proved most satisfactory in the author's hands. If the bleeding area is in the anterior portion of the septum, he applies *butyn* and *epinine* to anesthetize and then injects submucously a 1 per cent solution of *novocain*. Following this he makes an incision with the septal knife anterior to point of bleeding, then elevates the mucous membrane away from the cartilage and bone extending posteriorly at least 1 cm beyond the area of hemorrhage. This will usually control the average bleeding. However, he places in the nares on that side a pledget of cotton or gauze which is left *in situ* for 24 hours and then re-

moved; there is usually no subsequent bleeding.

In more severe types, especially if the bleeding is posterior, a **submucous resection** is necessary. This has proved effective in very severe nasal hemorrhage when other methods have proved of no avail.

Other Methods—Autohemotherapy, the injection of the patient's whole blood below the mucosa in the area of the bleeding, is suggested. It is worth trying in bleeding from Kiesselbach's area.

The author mentions **cauterization**, electric and chemical, and the use of **snake venom** which he thinks is of doubtful help. **Ligature of the carotid artery** is done when other measures fail and profuse bleeding persists.

In addition to the above measures, Riggs stresses that the patient should be urged to use a **bland ointment** 4 to 6 times daily, over many weeks. Three to 5 per cent **ammoniated mercury**, **yellow oxide of mercury**, **vaseline**, or **vaseline and lanolin** (anhydrous) are all useful.

Sinus Bleeding

Another source of epistaxis which is often overlooked is that of hemorrhage from the maxillary sinus. This is a relatively rare condition according to the literature, yet S. S. Hall and H. V. Thomas¹⁰ report 12 cases seen by them. They described the blood supply in detail and think trauma to a blood vessel in the sinus is the cause of the condition. They also associate it with hyperplastic diseases. The trauma may be induced by a violent blowing of the nose. A radical operation was performed in 10 cases with immediate control of the bleeding, however, the 2 unoperated patients got along as well. As a result of this, the authors think conservatism was

indicated; to wit, simple irrigation of the antrum for the removal of the clots.

SINUS DISEASE

Association with Dental Pathology—Dental pathology is frequently responsible for certain cases of reflex irritation of the eye and certain cases of uveal infection through lymphatic and vascular channels and it is also not infrequently responsible for certain reflex pain located in and about the ear and also from mechanical pressure certain otitic congestions. Harold T. Garrard¹¹ states that dental pathology is very commonly the source of antral infection and a secondary satellite frontal sinusitis, and reports several cases of involvement of both of these cavities which did not clear up until the dental infection focus was removed. Most often, but not always, the upper teeth affect the sinuses and the eye on the same side and the lower teeth are more apt to cause referred phenomena to the ear of the same side.

The correct solution of a given case requires discriminating judgment in weighing all factors involved and not entirely based on 1 or a few points, not even a negative x-ray which, at times, is deceiving. This solution is absolutely dependent upon the closest co-operation between the dentist and the physician with an open-minded attitude by both.

Ocular Disorders—Sinusitis may be the cause, unconsidered and neglected, of ocular diseases hitherto considered hopeless as to prognosis, according to F. W. Vandergrift.¹² Because he has found conservative suction douching of the sinuses a simple, painless and harmless method, he has adopted it as a routine diagnostic procedure with the result that many cases of sinusitis augmenting ocular disturbances have been discovered

before they went so far as to need more drastic care. To be as efficient as possible, the *suction douche treatment* should be preceded by *shrinkage of the nasal mucous membrane* and softening of the discharges by such methods as exposure to *infrared rays*.

Vandergrift uses the sinus douche method almost routinely in cases of refraction with asthenopia and headache, where a mild sinusitis aggravates the ocular distress. Correct glasses often fail fully to relieve the symptoms because congestion from the sinuses interferes with normal ciliary action. A mild sinusitis often accompanies the phorias (particularly exophoria). The sinus condition aggravates symptoms that arise from an otherwise harmless exophoria over which myopic correction and prism exercise appear to have no healing powers.

Radical sinus surgery is rarely necessary to relieve ocular distress, save life or vision. Most ocular lesions due to sinus infection are chronic, slow to begin and slow to increase. They can be treated by such conservative measures as the sinus suction douche affords. Positive findings by x-rays and transillumination are diagnostically valuable, but these methods have only a trifling worth if negative.

The suction apparatus consists of a T-shaped contrivance which connects permanently with a cold-water faucet. A tube goes from this to an indicator which records the amount of suction used. A second tube, from a Valentine irrigation bottle, contains the washing solution.

The amount of suction is registered on the indicator, the usual amount being between 5 and 15 pounds when the water is turned on. To the nasal tubes are attached hard rubber tips which fit into the nostrils. First one side of the

nose is washed out, the tips reversed then and the other side washed out.

If there is much pus in the first filled bottle, a second and third bottle are used until the washings are clear. Sometimes there is as much as 1 or 2 ounces of mucus and pus drained from each sinus

ORBITAL CELLULITIS

E D D Davis¹³ reports 54 cases of swelling of orbital tissues in 72 per cent of which the condition was due to supuration of the frontal or the ethmoidal sinus. He expresses the belief that if an orbital abscess is present, it should be *drained promptly* but that radical operation is seldom necessary. Cellulitis in children usually subsides under conservative treatment

SINUSES AND BRONCHIECTASIS

Sinus infection of one type or another was found by R L Goodale¹⁴ to be present in 73 per cent of 75 cases of bronchiectasis. The author thinks that those patients with chronic sinus disease are quite likely to suffer from further damage to the lungs because with the sinusitis they are more susceptible to colds which tend to increase the lower respiratory involvement

SINUS THERAPY

H D Rentschler¹⁵ expresses the opinion that the maxillary sinus leads all the other sinuses as to frequency of infection and as a cause of secondary disease and recommends for treatment a large intranasal opening through the inferior meatus. This has been sufficient in the majority of cases to relieve the symptoms of which the patient complained

Sinus Irrigation—H C. Rosenberger¹⁶ again calls attention to the natural opening route to the maxillary sinus. Irrigation of the sinus through this opening is a procedure which is anatomically correct, frequently applicable, not hazardous and one which certainly is feared less by the patient than puncture through the nasoastral wall. He anesthetizes both the middle and inferior meate, then probes for the natural opening. If he fails to locate this orifice readily he resorts to puncture below the inferior turbinate

Sulfanilamide — *Sulfanilamide* in the treatment of nasal and sinus infections has not produced the astounding results which characterize its use in combating infections elsewhere in the body. B J McMahon¹⁷ however, as a result of his experiments on rabbits believes that sulfanilamide should be as effective in the treatment of streptococcic sinusitis as it is in similar infections involving other structures. The drug given by mouth was recovered in substantial amounts from the tissues of the nose, sinuses and blood in most of the animals studied. The signs of sulfanilamide toxicity, he states, were hyperpnea, apathy, vertigo and spastic and flaccid paralysis

H P Schenck¹⁸ in reviewing the literature on the use of sulfanilamide in sinus disease, cited several cases reported by various authors wherein the drug was effective in the presence of sinusitis due to the hemolytic streptococcus. One case complicated by orbital cellulitis responded favorably when sulfanilamide was administered, yet in several cases its value was questionable. Most writers express the belief that in cases in which streptococci are present, operation should be barred in favor of medication with sulfanilamide and this should be given in large doses

Roentgen Treatment—Seven years' experience in the use of the *roentgen rays* in the treatment of *chronic sinusitis* has convinced F. E. Butler and I. M. Woolley¹⁹ that the roentgen treatment of chronic sinusitis has a definite therapeutic value in properly selected cases. When skillfully applied, it does no harm and causes no serious reactions. Nor does it interfere with subsequent surgery, should surgery later be indicated.

Butler and Woolley base their plea for a more general use of roentgen treatment in chronic sinusitis on clinical observations of more than 2000 treatments and on the study of roentgen therapy as applicable to any and all types of sinusitis, but they have noted that seldom is there a return of symptoms as severe as the original. Many patients have been able to withstand severe upper respiratory infection without the return of sinus symptoms.

Effects upon secondary symptoms have also been gratifying. Headache, neuritis, bronchitis and similar manifestations, traced to infected sinuses, have in almost every case cleared up after irradiation. Reactions have been negligible.

Roentgen treatment is not indicated in those cases of sinusitis, a good percentage of the total, which clear up spontaneously or yield readily to conservative methods. Efforts to relieve atrophic sinusitis have not met with success. Nor have benefits been obtained from x-ray irradiation of cysts or polyps. There have been several cases, however, where membranes underwent resolution without any change in the cyst. In a few other cases, polyps did not recur following sinus irradiation after removal of polyps.

The technic of treatment employed by Butler and Woolley is as follows: The eyes and nose are carefully protected by lead shields. For maxillary

sinuses, a port of 1.25 inches in diameter is employed. The central ray is directed posteriorly, medially and slightly superiorly, in order that there may be a cross-firing of the ethmoidal and sphenoidal sinuses. For treatment of the ethmoidal cavities, lead foil is applied so that only the ethmoidal sinuses on one side are unprotected. The central ray is again directed obliquely posterior so that it will cross-fire the sphenoidal sinuses. The frontal sinuses are treated through lead foil with appropriate openings. Each area is treated separately, with due care not to overlap the skin previously exposed.

All involved areas are treated on the same day. Better results have been obtained from the maxillary treatment when the ethmoidal sinuses are also treated—if they show any evidence of infection. Factors used are 120 kv., 5 ma., 4 mm. aluminum filter, 11 inch distance for 10 minutes through each port. This amount of irradiation is equivalent to 700 R with backscattering.

Most patients require only 1 treatment. However, all are asked to report back in 6 or 8 weeks. If the sinuses have not entirely cleared up but improvement has been noted, further treatment may be given. Caution must be used not to overtreat the skin.

Because it has the added advantage of greater penetration and much greater protection to the skin, Butler and Woolley have for the past 6 months treated some cases of chronic sinusitis with high voltage and filtration. In these cases the factors were 200 kv., 20 ma., 0.75 mm. copper and 3 mm. aluminum filter, 55 cm. distance for 10 minutes through each of 2 ports.

With this technic, only one side of the face is shielded with lead, except over the maxillary, ethmoidal and frontal sinuses on that side. The central ray is

again directed obliquely in order to cross-fire the deeper cells. The procedure is repeated from the opposite side at the same sitting. This dose is equivalent to 530 R. measured with backscattering (450 R. measured in air).

Both of the technics used apply only to adult patients with chronic sinusitis. When dealing with acute involvement or in treating children, the dose may be materially reduced.

ATROPHIC RHINITIS

Treatment—Because of the physiologic similarity in the nasal and vaginal mucosa and because of the pathologic similarity in atrophic rhinitis and atrophic vaginitis, *estrogenic substance (amniotin)* has been used in the nose. I. H. Blaisdell²⁰ prescribes this substance for home treatment as follows:

R Estrin 10,000 U 20
Sesame oil ad 300
Sig Spray nose t i d

He reports the results of treatment of 60 patients which he divided into 2 groups. Group I, true atrophic rhinitis, was comprised of patients who noted the onset of symptoms before the age of 20 years. Group II, secondary atrophic rhinitis, consisted of those who experienced symptoms after 20 years of age. For the most part patients in Group II have the familiar crusting with little or no odor, and if odor is present it is disagreeable but not as nauseating as in those in whom the condition developed before puberty. In those patients with secondary atrophic rhinitis (Group II), Blaisdell believes the nasal symptoms have generally developed from syphilis or sinusitis, although other factors, such as anatomic abnormalities of the septum, may be involved.

The patients in Group II, with secondary atrophic rhinitis, responded some-

what more satisfactorily to treatment with estrogenic substance than did those who developed the condition earlier in life. The correction of existing sinus conditions and structural abnormalities should be included in the therapy of cases of this nature.

INTRACRANIAL COMPLICATIONS OF SINUS DISEASE

A survey was made by Courville and Rosenvold²¹ of the infectious intracranial lesions secondary to diseases of the nasal air passages and accessory sinuses in a series of 15,000 cases in which autopsy was performed.

Frontal sinusitis was responsible for the intracranial lesion in 14 cases, extradural abscess in 4 cases, subdural abscess in 6 cases and cerebral abscess in only 2 cases. Septic thrombosis of the superior longitudinal (sagittal) sinus in this series was secondary to frontal sinusitis (2 cases). Septic meningitis, on the other hand, was a primary or direct lesion but was usually associated with and evidently consequent to some other frontogenic infectious lesion.

Ethmoiditis (18 cases) and sphenoiditis (22 cases) were frequently associated lesions and their most common intracranial complication was septic meningitis, which was present in 16 and in 20 of the respective diseases. Furthermore, in some instances, the association of sphenoiditis and otitis media observed at autopsy made it difficult to determine which lesion was responsible for meningitis. Extension into the cranial space was usually by way of the lamina cribrosa. Rhinogenic thrombosis of the cavernous sinus, present in a higher proportion of cases in other series, was present in only 3 cases. In all 3 cases sphenoiditis was present.

In 3 other cases thrombosis of the cavernous sinus was due to infectious lesions (boils or ulcerations) in the region of the nares

Intracranial complications consequent to maxillary sinusitis are rare, only 4 cases being found in our series. Direct extension with extradural and subdural lesions and with or without abscess of the temporal lobe is the rule. For reasons not entirely clear, maxillary sinusitis of dental origin is more apt to provoke intracranial suppurative lesions than any other type.

In general, an acute infectious lesion is more apt to result in intracranial complications than is a chronic one, a situation which differs from that present in otitis media and in mastoiditis, in which chronic disease is more prone to extend intracranially. Even to a greater extent than with otitis media, such rhinogenic complications are apparently much more common in males than in females (4 to 1).

Meningitis from the Sphenoid Sinus

R. W. Teed²² in an extensive review of the literature found 129 cases of meningitis from the sphenoid sinus. Following his study of the statistics, he draws the conclusion that while the sphenoid sinus is involved in about 15 per cent of clinical cases of sinusitis and in 33 per cent of pathologic cases it is nevertheless responsible for approximately 35 per cent of all rhinogenous intracranial complications. Evidence is presented which indicates that the spread to the meninges and venous spaces is predominantly vascular and that this extension is aided by the close anatomic relation of the vascular marrow spaces of the sphenoid bone with the infected mucosa of the sinus. The further relation between disease of the sphenoid sinus and of the pituitary body and insanity is observed,

with evidence that, in certain cases of mental aberration, resolution of the infection within the sphenoid sinus is remedial. With the recent increase of interest in this subject and with the knowledge of the symptomatology and associated pathologic changes in disease of the sphenoid sinus, the author hopes that the next few years will show a decrease in the deaths from this cause, not so much from treatment but from prevention by early attack on the diseased sphenoid sinus

PARANASAL SINUS MALIGNANCIES

According to New,²³ malignant disease of the paranasal sinuses is curable if proper and thorough treatment is employed, and in doing so he employs various types of *cauterization, surgical diathermy* and the use of *radium* and *roentgen rays*. He completely eradicates the tumor at one time, regardless of the resultant deformity. Loss of an eye or perforation of the cheek must be considered of secondary importance. Plastic surgery can correct these to a great extent if the tumors do not recur.

With regard to diagnosis, this authority points out that a dull, persistent pain in the face or upper jaw, usually made worse by lying down, may be attributable to a malignant tumor of the sinuses. He also urges that recent nasal obstruction or obstruction of the lacrimal duct, increased discharge with nasal bleeding, are symptoms. In doubtful cases, exploration of the sinuses is advised so that a fresh, frozen section of the tumor may be examined.

Bulging of the cheek of short duration, with pain, affecting a person of middle age, is practically always owing to a malignant tumor if the usual inflammatory conditions associated with the teeth

have been excluded. Inflammatory conditions of the antrum itself do not produce bulging of the cheek unless osteomyelitis is present.

The question of acute leukemia, agranulocytic angina, lymphosarcoma or carcinoma must be considered in cases in which a diagnosis of Vincent's angina has been made, for it is possible to find *Borrelia vincenti* in almost any ulcerated lesion about the mouth.

X-rays are valuable in the diagnosis of malignant tumors of the antrum. Types of tumor found in 91 cases of primary tumor of the antrum and 50 secondary tumors of the antrum are listed. Primary tumors are those which started in the antrum. Secondary are those which start in the upper jaw. This distinction of course, is not absolute because of the impossibility at times of determining where the tumor originated.

Selection of patients for operation is based on the location, and extent of the growth, the type of tumor and the presence or absence of metastasis, and in addition, on the patient's age, general condition and ability to return for observation. Recurrent adenocarcinomas and tumors of a low grade of malignancy are susceptible to treatment because they are less likely to metastasize than are other more highly malignant growths.

Patients who have extensive, primary, antral tumors of a highly malignant type have a better chance of recovery than those whose tumors are of the same size but are of a low grade of malignancy. The reason for this is that tumors of a high grade of malignancy can be destroyed by diffuse radiation whereas every particle of a tumor of a low grade of malignancy must be removed by surgical diathermy.

If lesions are of a low grade of malignancy, I feel that careful and thorough destruction with surgical diathermy at

the time of the first operation offers the best chance of clearing up the disease. He urges that if bone is involved, the periosteum must be destroyed in order to prevent recurrence. Unless a great deal of time and care are used, some tumor tissue will be left in place. In the presence of highly malignant lesions exploration should be made and enough of the tissue destroyed by means of surgical diathermy to establish very free drainage. Radium is then inserted at various points, directly into the tumor, through the wound. Complications such as meningitis, cerebral edema and hemorrhage are discussed.

The author reports the results of 295 cases of malignant tumor of the upper jaw and antrum in which operation was performed previous to 1929. Two hundred and thirty-six patients were traced, of whom 127 (53.8 per cent) were living without recurrence 5 years later. Of those who had tumors which were apparently primary in the antrum, 91 were operated on, 75 were traced and 30 (40 per cent) were living without recurrence 5 years later. Of the patients who had secondary antral tumors, 50 were operated on, 43 were traced and 23 (53.4 per cent) were living without recurrence 5 years later. Of those who had tumors of the upper jaw and palate, 154 were operated on, 118 were traced and 74 (62.7 per cent) were living without recurrence 5 years later.

Similar good results in a smaller series of cases were reported by R. C. Martin²¹. He states that of the 5 patients with malignancy of the nose, 1 was operated on and has remained well for 6 years. One received a combination of *radon* and *x-ray therapy* and is living after 2 years 6 months, but recurrence is probable in this case. Two were treated by roentgenotherapy, both of

whom are living and well after 2 years 3 months, and 4 years 7 months. One was treated by radium and is alive and well after 2 years 5 months.

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PEDIATRICS

Edited by A GRAEME MITCHELL, M.D.

ANEMIA IN CHILDREN

By CLARE R. RITTERSHOFER, A B, A M., M.D.

The Mechanism of Anemia—Hugh Josephs¹ looks upon anemias as due to physiologic processes which have been brought about by various etiologic factors. These effective factors may be constitutional or intrinsic, or some factor such as infection or other disease involving directly or indirectly the formation or destruction of blood, and such extrinsic factors as intoxication or deficiency. These physiologic processes may be classified in 4 groups: (a) Hemoglobin synthesis, (b) hemopoietic activity, (c) hemolysis, and (d) disturbance in maturation.

Hemoglobin deficiency may result from lack of material for its formation or from failure of synthesis. Because of the success of iron therapy and because the etiologic factors associated with the more severe grades of hypochromic anemia are such as to lead to iron deficiency, there is a tendency at the present time to regard hypochromic anemia as synonymous with iron deficiency anemia. The etiologic factors associated with iron deficiency are: Prematurity, anemia of the mother during pregnancy; rapid growth, diet low in iron, gastrointestinal disturbance leading to interference with absorption as in dysentery and celiac disease, or associated with hypochlorhydria, loss of iron from the body as in hemorrhage or in chronic blood loss.

The reticulocyte count offers an accurate and exact measure of the amount

of regeneration occurring in hemopoietic tissue and should be a necessary part of any study of the blood. Signs of increased regeneration in the absence of hemorrhage or of specific stimulation should always arouse a suspicion of the presence of increased hemolysis. When regeneration is intense, a few nucleated red cells may appear as at the time of beginning recovery after a severe hemorrhage, an acute hemolytic crisis, or in the recovery phase of anemia of the newborn. Lack of adequate regeneration is shown by reduction in platelets, and white cells, absence of nucleated red cells, and a reticulocyte percentage that is lower than should be expected under the conditions that exist at the time of examination. Lack of adequate regeneration may occur in 3 conditions: (1) Aplastic anemia, (2) Bone marrow replacement, (3) Lack of adequate stimulation.

1. In aplastic anemia there is a failure of development of blood cells not only in the bone marrow itself but also in those places where extramedullary hemopoiesis might occur. The etiologic factors causing aplastic anemia are not understood. The use of repeated transfusions has occasionally been followed by recovery.

2. In the case of bone marrow replacement the blood picture may have no resemblance to aplasia whatever, even though the normal hemopoietic tissue may be completely destroyed. This may

be due to the development of extra-medullary foci of blood formation, so that combined with some elements of hypoplasia are others pointing to intense activity. Examples of bone marrow replacement are seen in tumor metastases to the bone marrow, in osteosclerosis, in generalized xanthomatosis, occasionally in Hodgkin's disease and in congenital syphilis. The characteristic picture is that of reduction of the blood elements with marked immaturity of white and red cells. Earlier in the course there may be no change except possibly a slight anemia with or without a reduction in platelets and tendency to petechiae.

3. In the case of lack of stimulation there is a tendency to an unregenerative form of anemia, often with a low white count and low platelets. These conditions may be found in cirrhosis of the liver, splenic vein thrombosis, Gaucher's disease, Hodgkin's disease and a group of cases classified under reticuloendotheliosis.

One of the most common causes of lack of regeneration or hypoplasia is infection. In chronic cases there is no treatment that can be relied upon to influence the process. In acute septic infections hypoplasia is not so very uncommon though the most striking finding may be reduction in the myeloid cells and the case be called agranulocytosis. In infections there may be in addition to hypoplasia an increased hemolysis and a tendency to immaturity.

Hemolysis—Transitory increase in the rate of blood destruction up to 2 or 3 times the normal is very common, but generally is of little importance. It is usually not difficult to recognize increased hemolysis when this is the dominant process but it must be emphasized that jaundice may be absent in such cases especially in infancy.

Disturbance in Maturation—Erythroblasts may occur in the blood stream in a disturbance of erythropoiesis interfering with maturation, the degree of immaturity depending on the depth of the disturbance. The author divides the erythroblastosis into 4 levels: (a) That in which normoblasts appear only on the occasion of excessive stimulation or during the crisis of a hemolytic anemia; (b) that characterized by the more or less continued presence of normoblasts with occasionally more immature erythroblasts; (c) that in which immature erythroblasts form an integral part of the picture, and (d) that in which there may be present the forerunners of the red cells, the macroblasts or megaloblasts. The major hemolytic anemias of constitutional origin may be grouped in accordance with the first 3 levels: Congenital hemolytic jaundice at level 1; sickle cell anemia at level 2, and Mediterranean anemia at level 3. In the cases dependent primarily on constitutional factors, the immaturity rarely reaches the level represented by the presence of megaloblasts. The cases in which macroblasts or megaloblasts are a feature are those in which the principal factors are infections or nutritional. Examples are severe anemias associated with syphilis, sepsis and malaria, but particularly in von Jaksch's anemia. The author emphasizes that the presence of 1 process affecting 1 element of the blood may often affect others. Thus increase in regeneration may be accompanied by increase in white cells and erythroblastosis may be accompanied by marked immaturity of the white cells, to which the term pseudoleukemia has been given. This picture is seen especially in septic infections in small babies and is seldom seen beyond infancy. The picture is that of extreme immaturity of red cells with

relatively low reticulocyte counts, leukopenia, and thrombopenia.

Classification of Anemias—A pathogenetic classification of the anemias has been suggested by E. Krumbhaar² as follows

CLASSIFICATION OF ANEMIAS

- I. Mainly Due to Disorders of Erythrocyte Formation
 - (a) Insufficient formation in bone marrow, usually normocytic (aplastic, myelophthisic, due to physical injury, etc.)
 - (b) Defective formation
 - 1 Erythroblastosis
 - 2 Spherocytic (hemolytic jaundice)
 - 3 Ovalocytic
 - 4 Sick cell anemia
 - 5 Poikilocytic, normochromic or hypochromic (deficiency of diet, vitamin or hormone, hookworm, chlorosis, "idiopathic," etc.)
 - 6 Macrocytic (pernicious, sprue, pellagra, secondary to some gastrointestinal or liver disorders, etc.)
- II Mainly Due to Blood Loss
 - (a) Hemorrhage from trauma (acute blood loss)
 - (b) Chronic or intermittent bleeding, as in gastrointestinal and genitourinary tract
 - (c) Abnormal blood vessels or other blood constituents (purpura, hemophilia)
- III Mainly Due to Excessive Destruction
 - (a) Hemolytic infections, toxins, poisons, etc.
 - (b) Secondary to defective formation
 - (c) Unknown nature (Jedeter's) (Banti's)

Diagnostic Aids—C. A. Doan, C. A. Moore and T. F. Ross³ stress the increasing significance of the bone marrow punctures both from a diagnostic as well as prognostic point of view. Sternal puncture is recommended as a simple medical procedure. A suitable site in the body of the sternum opposite the third or fourth interspace is chosen, prepared with surgical skin aseptic technic, and infiltrated with 1 per cent novocain,

including the subperiosteal area, if local anesthesia is desired. A stiff, 17-gauge spinal puncture needle is inserted at a 45-degree angle with firm, steady pressure. Remove the obturator and insert a tight-fitting 10-cc. or 20-cc. syringe, and suction marrow and blood just to the bottom of the syringe connection. Withdraw the needle with syringe still attached and expel the content of the needle onto a clean glass slide.

Iron Deficiency Anemia

A comprehensive review of the literature of the iron deficiency anemias including the hypochromic anemia of infancy and childhood has been made by C. W. Heath and A. J. Patek, Jr.⁴

Incidence of Anemia in Preschool Children—Thomas Colver⁵ attempted to determine the degree and frequency of preschool anemias in South London by doing hemoglobin estimations on 310 children. The results showed that in relation to the "iron standard" the average South London child up to the age of 3 years is anemic. The "iron standard" is thought to represent the optimum hemoglobin level in infancy (6 to 12 months, variations of ± 10 per cent [Haldane] being regarded as within the limits of normality). According to Mackay and Usher 86 per cent, Haldane (11.7 Gm. Hb. per 100 cc.) is the mean level thus attained. By comparison with the lowest hemoglobin standards anemia was present in 36 per cent of the 1-year infants, 27 per cent of those aged 2, 20 per cent of those aged 3, and 15 per cent of those aged 4. By comparison with the "iron standards" this incidence is doubled. Severe anemia was uncommon after 3 years of age, and anemias of any type after 4 years.

In an analysis of red cell counts and hemoglobin determinations on 2521 patients at the Children's Hospital in Cin-

cinnati over a 2-year period, C. Rittershofer⁶ has shown that the most frequent type of anemia occurring in that institution is the nutritional anemia of infancy and early childhood. Using a mean hemoglobin per cell value of 25 micromicrograms as the lower limit of normal and 20 micromicrograms as representing a severe type of nutritional anemia, it was pointed out that over 50 per cent, or 269 out of 538 children, between the ages of 6 months and 2 years suffered from a mild or borderline nutritional anemia and that 17.5 per cent of those in the same age group, or 95 of 538 patients, had a serious type of nutritional anemia. Compared with the other age groups the period from 6 months to 2 years contains by far the greatest number of these patients.

A study was made by B. Munday, M. L. Shepherd and associates⁷ to determine hemoglobin differences between white and negro infants. 2843 blood studies were made on 335 white babies and 1145 studies on 140 negro babies. The average values of hemoglobin for the white infants were from 0.5 to 1 Gm per 100 cc of blood higher after the fourth month than those for the negro infants during the remainder of the first year of life. During the initial drop and up to the end of the third month no racial differences were observed in the hemoglobin curves for the 2 groups. No significant racial difference between the red blood cell values of the white infants and those of the negro infants could be established.

Retention of Iron in Childhood—James H. Hutchison⁸ made a series of iron-balance studies on inpatients at the Royal Hospital for Sick Children in Glasgow in an attempt to obtain more information on the absorption and fate of ingested iron in the body. The results of these studies demonstrated that

the body is capable of retaining large amounts of iron administered in the inorganic state, and that the necessity for large doses of iron in the treatment of nutritional anemia is not dependent on the poor absorption of iron salts from the intestine. Further, that high rates of iron retention can be maintained over long periods with resulting accumulation in the body of large amounts of iron.

An explanation for the massive doses of iron which are needed in these cases is based on the assumption that iron once deposited in the tissues is not available for the regeneration of hemoglobin, unless it has been derived originally from the destruction of hemoglobin in the body, and that the great bulk of iron absorbed from the intestine during massive dosage with inorganic salts would not be available as it would first find its way to the liver, where it would be stored and thus rendered inactive for hemoglobin synthesis. From this it is supposed that only by giving massive doses of iron can the rate at which it is stored by the liver be overcome and the excess iron be pushed past the liver directly into the blood serum, from which it may be utilized for hemoglobin formation.

According to W. Fishbein, J. K. Calvin and J. Heumann,⁹ grape juice aids in the regeneration of hemoglobin and is a good source of nutritionally available iron. In their study 10 ounces of grape juice when added to the regular diet produced a consistent gain in the hemoglobin.

Nutritional Anemia—H. W. Fullerton,¹⁰ in discussing the iron-deficiency anemia of late infancy points out that the greater degree of anemia present in artificially fed infants than in breast-fed infants is probably due to a low iron retention; that infants of anemic mothers are slightly, if at all, more liable to de-

velop anemia than those of nonanemic mothers; that the anemia of premature infants and twins is a direct consequence of 2 factors—a low iron content at birth and rapid growth. The common infective illnesses of infancy produce a rapid fall in hemoglobin level and may inhibit blood regeneration for a considerable time after the disappearance of clinical evidence of infection. Further, that the breast-fed infants of normal birth weight and free from all illnesses should not theoretically develop an iron deficiency before the age of 9 months. Other factors which might cause an anemia during this period are achlorhydria, low blood volume, severe infections and a low dietary iron intake. In view of the great frequency of anemia in infancy and the knowledge of its etiology, it is suggested that a hemoglobin estimation be made in all infants at the age of 3 months; where this is not possible a course of iron therapy should be given routinely at the age of 3 months to all infants of birth weight less than 7 pounds, and in cases of artificial feeding. Iron therapy should be instituted after illnesses of an infective nature, and should be continued for at least 2 or 3 months.

Symptoms—According to the REVIEWER (*loc. cit.*), the clinical recognition of nutritional anemia is not easy unless the hemoglobin is below 8 Gm per 100 cc or the hemoglobin per cell value is below 20 micromicrograms, in which case the skin is apt to have an ivory yellow or sheet white pallor, most marked in the ears and face. The color of the lips is misleading.

The blood picture of nutritional anemia is that of an anemia of the hypochromic microcytic type. The red cell count may be high, low or normal. The hemoglobin is reduced to a varying degree. The less severe anemias show a fall in the hemoglobin with little or no diminution

in the red cell count, while in the severe cases the hemoglobin values are still lower and a small drop in the red cell count occurs, or the red cell count may be elevated and the hemoglobin only slightly reduced, in which case it is important to rely upon the figure for the mean hemoglobin per cell since this clearly points out the hemoglobin deficiency. Examination of the smear shows a central pallor of the red cells. Other findings are a microcytosis, a low volume index, and a diminution in cell volume.

L. Parsons, E. M. Hickmans and E. Finch¹¹ endeavored to test out and extend the views on microcytosis and congenital anemia by means of controlled experiments on normal stock rats because the nutritional anemia in the rat exhibits the same features as regards hemoglobin values, number of red cells, and response to iron therapy as the nutritional anemia of infancy. When a special iron-deficient solid diet was fed to rats, it resulted in the development of polycythemia and microcytosis although the hemoglobin remained normal—findings which it is suggested are the first signs of an iron deficiency anemia. The authors believe that in all iron deficiency anemias the bone marrow hypertrophies in an attempt to produce large numbers of small cells to hold the available hemoglobin and thus to offer the largest possible surface area of hemoglobin for gaseous exchange. This view is confirmed from the fact that in the course of the cure of nutritional anemia of infancy by the use of iron, Hagen's phenomenon occurs, *i e.*, before the hemoglobin reaches a normal figure the red cell count may exceed 6 million cells but when the hemoglobin does become normal the red cells become reduced to 5 million. One important difference between the human mother and the rat

has been observed. The human mother can sacrifice her own hemoglobin for the sake of the child, and although she may become profoundly anemic herself, more often than not gives birth to a child whose blood is normal, whereas in none of the rat experiments has any pronounced diminution in hemoglobin in the mother rat occurred. This congenital nutritional anemia of the rat is microcytic in type and becomes progressively worse if milk feeding is continued beyond the lactation period.

Their findings support the suggestion that the infants of women whose diets during pregnancy are low in iron or who suffer from an iron deficiency anemia may show a congenital nutritional anemia.

Treatment of the Iron Deficiency State—W. Dameshek¹² states that the most popular form of iron in this country has proved to be *ferrous sulfate* given in dosage of 1 Gm. or less per day. A special coating is used to prevent the ferrous sulfate from being oxidized to the ferric form. When using ferrous sulfate, diarrhea does not occur; in fact a slight degree of constipation may result. That a combined copper and iron deficiency is occasionally present is possible, but this does not warrant the routine use of copper in hypochromic anemia, particularly in infancy, where routine treatment with copper has been actively advocated. At the present stage of our knowledge, therefore, the author feels that it is better to refrain from the use of copper unless it seems essential to increase the hemoglobin concentration in a case of hypochromic anemia refractory to all types of iron treatment.

Within the last few years it has been demonstrated repeatedly that the hypochromic anemias are benefited by the use of iron, but the question of the kind of iron preparation and the dosage has not been agreed upon. From the literature

it appears that the ideal form of iron in the treatment of infants should meet the following requirement, *viz.*, it should be an inorganic ferrous form in solution and should be given orally. R. Stephenson¹³ has carried out a controlled study on an orphanage group of 64 healthy white boys and girls with the design of learning (a) whether all healthy infants of this age range who live under good conditions exhibit the reported hypochromia, (b) how far adequate iron therapy raises their hemoglobin level; (c) the comparative efficacy of varying doses of ferric and ferrous forms of iron; (d) for what length of time a maintenance dose of supplemental iron is indicated. The iron preparations chosen were iron and ammonium citrate in solution and an elixir of ferrous sulfate.

Half of the infants were each given 30 grains of *iron and ammonium citrate* (about 340 mg. of metallic iron) daily; the control infants were each given 6 grains of ferrous sulfate (about 78 mg. of metallic iron) daily. Therapy was continued for 3 months, the effects being checked by estimations of red cell count, hemoglobin and red cell volume. The results showed that the ferrous iron proved to be as effective as the ferric as judged by the increase in the hemoglobin levels, and that 14 Gm. of hemoglobin per 100 cc. of blood is the optimal level to be expected from administration of these forms and doses of iron continued for 3 months for infants of this age period. Further, that the trend of the hemoglobin level was downward in those infants whose medication was discontinued at the end of 3 months whereas it was upward in those for whom medication was maintained. The traces of copper present as contaminants of the iron preparations were not thought to have as much effect as the generous supple-

ments of iron. The ferrous iron was found to produce a maximum effect with much smaller doses than ferric, and it caused no gastrointestinal disturbance. The author suggests that 6 grains of ferrous sulfate might be an adequate dose to maintain hemoglobin at an optimum level up to 2 years of age.

H. M. M. Mackay and L. E. Jacob¹⁴ treated a group of children with iron deficiency anemias with a stable solution of ferrous sulfate in varying doses. The mixture used was:

Rx Ferrous sulfate	gr $j\frac{1}{2}$
Dilute hypophosphorus acid	$\text{m}\times 1\frac{1}{4}$
Dextrose	gr xv
Chloroform water to	\mathfrak{zj}

The method of preparation is as follows. Dissolve the dextrose in some of the chloroform water, add the dilute hypophosphorus acid. Dissolve the ferrous sulfate in some chloroform water and add to dextrose solution. Make up to volume with chloroform water. This mixture will keep for over 2 months at room temperature without any precipitation.

The series of 26 patients was treated 3 times daily in 1 dram or 2 dram doses which were always begun gradually, the full dose being reached in 3 to 5 days. Given in this way it was well tolerated, and there were no complaints of loose stools or colic. Part of the group received 9 grams (0.58 Gm.) of ferrous sulfate daily while the others received $4\frac{1}{2}$ grams (0.29 Gm.) of the same mixture. The results obtained with both doses of ferrous sulfate were satisfactory as each produced an average daily rise in hemoglobin level of almost 1 per cent over the first 3 to 5 weeks of treatment. In each group in spite of good response to treatment, the average time taken to reach 80 per cent hemoglobin was about 50 days, and individual cases took much longer. The presence of an

intercurrent infection nearly always necessitates more prolonged treatment. Their results gave them the impression that during an intercurrent illness there is considerably more likelihood of a rise in hemoglobin level if a ferrous salt is administered rather than a ferric salt. The amount of iron in $4\frac{1}{2}$ grams of ferrous sulfate is about 60 mg. Among the causes for the inadequate treatment of anemia in infants with iron and ammonium citrate and other ferric salts are (a) the large doses desirable and the fact that when these large doses are suddenly started, gastrointestinal upsets are not unusual and (b) that long periods of treatment are often necessary. The author recommends for therapy a ferrous salt and for prophylaxis on a wide scale the cheap and stable iron and ammonium citrate which is effective and well tolerated.

Iron-Cobalt Therapy—K. Kato¹⁵ noted that the clinical trial of iron-cobalt combination treatment as applied to physiologic and nutritional anemia of infants yielded favorable results in 76 per cent, or 42 out of 55 infants, treated in this manner. Cobalt, when administered in a dosage approximately one-tenth that of iron, appears to accelerate the formation of red blood cells and hemoglobin. Its action appears to be an effective catalyst in increasing both the hemoglobin content of the blood and in accelerating the formation of erythrocytes. Histologic examination of the tissues of animals showed a hyperplasia of the cellular marrow elements. Hematologically the increase in the red cell count, hemoglobin, and packed cell volume under iron-cobalt treatment described a parallel course probably the result of the accelerated erythropoiesis. The optimum therapeutic dose of cobalt-sulfate is $\frac{1}{25}$ to $\frac{1}{12}$ grain (25 to 50 mg.) daily for infants under 2 years of age,

administered in combination with $7\frac{1}{2}$ grains (0.5 Gm.) of assimilable iron. It is to be used only as an adjunct to iron therapy during the first 2 or 3 weeks of active treatment of simple nutritional anemia as its action is probably only that of a catalyst.

Liver Therapy in Secondary Anemia—Probably because liver is such a valuable material for the treatment of pernicious anemia, great emphasis has been placed on the use of liver and liver products in secondary anemia. A secondary anemia fraction for liver which is active in hemoglobin regeneration in dogs suffering from hemorrhagic anemia has been described. Evidence has accumulated tending to show that liver promoted a definitely greater regeneration of hemoglobin than did the addition of an amount of inorganic iron equivalent to that contained in the added liver. The response was no greater with iron plus casein than with iron alone, which eliminates the possible protein effect of the liver. In spite of these facts high levels of inorganic iron have proved very effective in the treatment of a variety of hypochromic anemias. There is still a question about the reason for the need of such large amounts. It is probable that the high intake of iron salts supplies added amounts of copper as a contamination, but this has not been demonstrated beyond question. According to E. B. Hart, C. A. Elvehjem and G. O. Kohler¹⁶ there is evidence in the literature that liver extract is a most excellent source of most of the factors in the B complex, and it emphasizes the importance of recognizing the value and limitations of each ingredient in such mixtures. In the case of anemia due to a simple deficiency of iron and copper, small doses of iron and copper work very efficiently with no other additions. When milk constitutes a large part of the diet,

it supplies ample amounts of the other nutrients needed for hemoglobin formation. These authors concluded that the effectiveness of whole liver in the treatment of nutritional anemia in rats induced by a milk diet is directly proportional to its available iron and copper content.

In a study carried out by P. B. Pearson, C. A. Elvehjem and E. B. Hart¹⁷ to determine the effect of 9 different proteins on the rate of hemoglobin regeneration in nutritional anemia, it was found that the proteins of liver, casein, egg albumin and soy bean oil meal are consistently effective in building hemoglobin. When the intake of iron and copper is adequate to permit hemoglobin formation at the maximum rate, no special hematopoietic property in addition to their protein content can be ascribed to any of these materials. There is no evidence that liver is more effective for hemoglobin formation than are proteins of good quality.

Anemia Resembling Pernicious Anemia

J. Adams and I. McQuarrie¹⁸ reported a case of "pernicious-like" anemia in a child which closely resembled the adult type. The patient completely recovered following the use of **liver extract** (antipernicious-anemia factor, Lederle). Since special tests to determine the presence of the intrinsic factor were not done, it was not felt that a diagnosis of true pernicious anemia was justifiable. In this case the pathogenesis of the anemia was obscure, since several features such as vomiting, infection, or a disturbance in gastric function might have contributed to it. Since the onset of the patient's anemia was preceded by an acute febrile illness, it seemed that the latter may have been responsible for a transient functional disturbance of the mechanisms

normally responsible for the production of both free hydrochloric acid and the intrinsic antianemic factor.

Acute Hemolytic Anemia (Lederer Type)

The outstanding features of the acute hemolytic anemia described by Lederer were acuteness of onset, evidence of rapid erythrocyte destruction, marked bone marrow regeneration, recovery following transfusion and the absence of sequellae. E. H. Baxter and M. W. Everhart¹⁹ report another case featured by acute onset, prostration, leukocytosis, and rapidly developing anemia which showed evidence of rapid blood destruction and bone marrow regeneration. The patient responded to blood transfusions.

R. Greenthal²⁰ reported a case of acute hemolytic anemia whose etiology was presumably a streptococcus angina with streptococcus sepsis. In the anemia described by Lederer, the etiology was obscure but probably infectious. Otherwise this case might be so classified. Sulfanilamide was used in the treatment of the infection in this case. It was impossible to state whether the sulfanilamide in this case prolonged or intensified the blood condition. The anemia was successfully combated by several blood transfusions.

Sickle Cell Anemia

A. G. Harden, Jr.,²¹ has reported 2 further diagnostic features in the syndrome of sickle cell anemia. The first

is the so-called hair-on-end appearance in roentgenograms taken of the skulls of patients with long-standing involvement and, secondly, widespread vascular changes. The x-rays of the skulls of the 2 patients reported showed an increase in the thickness of the calvarium in all areas with a loss of continuity of the outer table of the skull. The marrow cavity had been replaced by radially placed bone formation simulating many individual hair shafts standing erect. The eye grounds had an abnormal vascular appearance. The veins were greatly dilated and at the same time tortuous. The arteries were also tortuous but to a lesser extent. The caliber of the vessels decreased evenly and not irregularly. It was felt that the vessels were congenitally abnormal.

Aplastic Anemia

G. B. Peat²² reported a case of aplastic anemia in a child which had benefited by weekly transfusions.

Anemia Neonatorum

H. Lehdorff²³ describes an anemia neonatorum occurring in full term healthy infants at the end of the first week of life. The anemia develops suddenly and disappears without any therapy. The blood picture is that of a hyperchromic anemia with a high color index. There are no changes in the red cells. The author speculates on the factor producing this picture and suggests a toxic agent different from all known factors.

CHICKENPOX

By ROBERT A. LYON, M.D.

Unusual forms of chickenpox eruptions have been described by G. W. Ronaldson and W. H. Kelleher.²⁴ Prodromal rashes, appearing a day or two

before the typical eruption, occurred in 3 children. These eruptions were of a fine papular or erythematous character. It was impossible to blanch these rashes

with convalescent serum of chickenpox patients but no other cause of the lesions than the chickenpox infection could be ascertained. Modification of the typical chickenpox eruption with the production of small lesions, which are delayed in development or do not progress normally, has been observed in patients convalescent from other diseases, in those who have received intracutaneous injections of varicellous lymph, or deep injections of convalescent serum. Bullous, gangrenous and hemorrhagic forms of eruption have been noted in patients with coexisting diseases. The close relationship between herpes zoster and varicella make certain atypical forms of either disease difficult to diagnose and it is possible that the two diseases may occur together.

Complications — Of the complications of chickenpox, severe infections of the skin are the most common. Such a case has been reported by H. S. Banks and J. E. McCartney.²⁵ A child, 4½ years of age, developed gangrenous lesions on the skin 4 days after the beginning of the chickenpox eruption. A single large ulceration and a few smaller ones spread rapidly and were accompanied by severe toxemia. The patient died within 48 hours and a hemolytic streptococcus was recovered from the blood and from the infected tonsils. The latter region was suspected as the source of the secondary infection. The author found that 2 general types of skin complications of chickenpox had been reported, one of the nature described above in which there was a rapid onset and extensive necrosis and the other which is much slower in its development and is characterized by numerous small ulcers. The streptococcus and diphtheria bacillus have been described most frequently in previous reports as the infecting agent.

Severe *gangrenous lesions* resulting from the simultaneous occurrence of thrombocytopenic purpura and chickenpox were observed recently by A. V. Stoesser and W. W. Lockwood.²⁶ A child of 3 years developed a bluish discoloration on the thighs on the fifth day after the appearance of the chickenpox. The lesions spread to the other limb and severe gangrene, necrosis and sloughing occurred, so that it became necessary to amputate portions of both legs. Evidence of acute thrombocytopenic purpura was discovered shortly after admission of the patient but repeated blood transfusions did not check the course of the gangrene. It was suggested that an abnormal sensitivity to chickenpox virus might have been an etiologic factor.

Complications of the nervous system following chickenpox have been observed more frequently during the past decade. One reported by D. MacIntyre and H. L. W. Beach²⁷ consisted of an acute encephalomyelitis occurring in a girl 7 years of age. The patient developed weakness and anesthesia of the legs and urinary incontinence a week after the onset of the chickenpox. A week later the muscle power in her hands became weak and a loss of sensation occurred in the same locality. Two days later she complained of a severe headache and her neck became rigid. The following week, which was 1 month after the onset of chickenpox, severe pain developed in the left eye with a loss of vision. All of these symptoms slowly disappeared and when the child was re-examined 8 months later she was found to be in good health. Complications of the central nervous system following chickenpox tend to be mild and are usually followed by complete recovery.

Three patients with central nervous system complications of chickenpox have

been described by O. A. Faust.²⁸ One boy, 9 years of age, developed meningeal symptoms with the cerebrospinal fluid containing 1000 cells, mostly of polymorphonuclear type, on the eighth day before the rash of varicells appeared. The second and third patients developed encephalitic symptoms, in 1 child 4 days before the onset of the rash, and in the other patient on the fourth day after the onset of the illness.

Encephalitis following chickenpox in a 3-year-old boy has been reported by C. F. Walcott.²⁹ Symptoms of the complication, which first appeared on the fourth day of the illness, consisted of lethargy, ataxia, an absence of some of the tendon reflexes of the legs and stiffness of the neck. The cerebrospinal fluid was normal. Within 11 days most of the symptoms had subsided and the patient made a complete recovery.

DIABETES MELLITUS IN CHILDREN

By WALDO E. NELSON, M.D.

Diagnosis—A. H. Kantrow and J. D. Boyd³⁰ suggest that an insulin tolerance test may prove of value as a means of distinguishing diabetes mellitus and may be of as much importance as the dextrose tolerance test. The test as described by the authors consists of the administration of one-fourth unit of insulin per kg. of body weight and the determination of the blood sugar level before and at 4 subsequent half-hour intervals. The maximum reduction in the nondiabetic subject is observed in the first half-hour, whereas in the diabetic subject the fall is prolonged into the second or third half-hour or longer. This peculiarity of response appears to be inherent in the diabetic organism and is not determined by the initial blood sugar level, nor is there evidence that the nature of the response is altered by treatment of the disease.

According to M. Cooperstock and J. M. Galloway³¹ the 1-hour, 2-dose dextrose tolerance test of Exton and Rose is as advantageous for use with infants and children as with adults. The advantages claimed are those of specificity, time saving and convenience. The principle of the test is based on the fact that

when normal human beings are given repeated doses of dextrose, the insulin-glycogen mechanism operates in such a manner that either hypoglycemia or little or no change in the blood sugar level is produced, in contrast to the failure of this mechanism in diabetes in which hyperglycemia results from repeated administration of dextrose.

The technique of the test as employed by Cooperstock and Galloway is as follows. The test is performed after an overnight fast in the case of children who are receiving 3 meals daily. In infants who are receiving a formula, the early morning feeding is omitted prior to the test. A fasting blood sugar is taken, and the dextrose is administered in an amount equal to 1.75 Gm. per kg. of body weight in a 15 or 20 per cent solution. In the case of infants weighing less than 7 kg., a minimum total dose of 10 Gm. is employed. Blood is taken at the end of one-half hour for the determination of the sugar level and the dose of dextrose is repeated. One-half hour after ingestion of the second dose of dextrose, a third sample of blood is taken. The authors have found that the micromethod for the determination

of the blood sugar level is entirely satisfactory. Specimens of urine are obtained before the test, at one-half hour and at the end of 1 hour for examination of sugar content.

The criteria of the normal response to the 1-hour, 2-dose dextrose test, as established by Exton and Rose, are as follows:

- 1 Values of blood taken after fasting are within the normal limits of the particular method employed
2. The rise in the blood sugar level does not exceed 75 mg in the 30-minute sample
3. The amount of blood sugar in the 60-minute sample is less or the same or does not exceed that in the 30-minute sample by more than 5 mg
- 4 All samples of urine must have negative reactions to Benedict's test.

Gould and others have modified the criteria for diagnosis of diabetes and state that the condition may be correctly diagnosed if at least 2 of the following 3 conditions are encountered: (a) A blood sugar value during fasting which exceeds 120 mg; (b) a level in the half-hour tests which exceeds the level for the fasting specimen by 50 mg. or more, and (c) a blood sugar level at 1 hour which exceeds the half-hour level by 30 mg or more. These criteria were fulfilled by the diabetic children in the author's series in all but 2 instances, in which low, flat curves were obtained in the early, untreated state and in which high values during fasting were obtained months later. They did, however, have 2 patients with nondiabetic conditions whose responses to the tests fulfilled these criteria. One of these patients was an epileptic and the other had clinical findings of hyperthyroidism.

Technic for an intravenous glucose tolerance test has been described by T Crawford³². The dosage of glucose employed is 0.5 Gm per kg. of body weight, injected as a 20 per cent solution

in 0.9 per cent sodium chloride. Food is withheld for 8 hours prior to the test. A fasting specimen of capillary blood is taken before the glucose is injected and samples of blood are then taken at 2 minutes, 15 minutes, 30, 45, 60, 75, and 90 minutes after the end of the injection. The bladder should be emptied before the injection is given and again when the last specimen of blood is taken. Carbohydrate tolerance is gauged by the time required for the return of the blood sugar to the normal fasting level. It is stated that if the fall to 100 mg. per 100 cc. occurs in less than 45 minutes in children between 2 and 10 years of age, or in less than 60 minutes in children over 10 years of age, then increased tolerance is present. If, on the other hand, the fall to 100 mg per 100 cc. is delayed beyond 60 minutes in children under 4 years of age or beyond 75 minutes above that age, then there is some indication of decreased carbohydrate tolerance. While the test shows a higher degree of constancy for the individual than does the oral test, it is not recommended for general use but rather for special cases and in investigative work.

Diet—The idea is becoming more generally accepted that the dietary allowance of diabetic children may be varied within a fairly wide range without loss of tolerance as measured by the insulin required. Additional data to support this thesis are supplied by W. E. Nelson and D. Ward³³. Figure 000 is a summary of their observations on a diabetic child and shows the effects on the blood sugar and urinary sugar of changes in diet when the amount of insulin injected daily remained unchanged. No essential differences were found in the sugar content of the blood or the urine with diets containing 100 Gm of carbohydrate and 164 Gm. of fat, in contrast to diets containing 200 Gm of

carbohydrate and 120 Gm. of fat, when the amount of insulin injected each day remained unchanged. When the carbohydrate was increased to 300 Gm. and the fat reduced to 75 Gm., the level of the blood sugar and that of the urinary sugar were higher. However, the excretion of sugar was at no time in proportion to the increase of ingested car-

of measured diets for diabetic children: (a) Control of the child's growth; (b) insurance of a balanced dietary intake; (c) instruction of the child by experience with the content of an adequate diet; (d) proportionate distribution of the diet in the various meals, and (e) the psychologic effect of aiding in training the child in self-discipline.

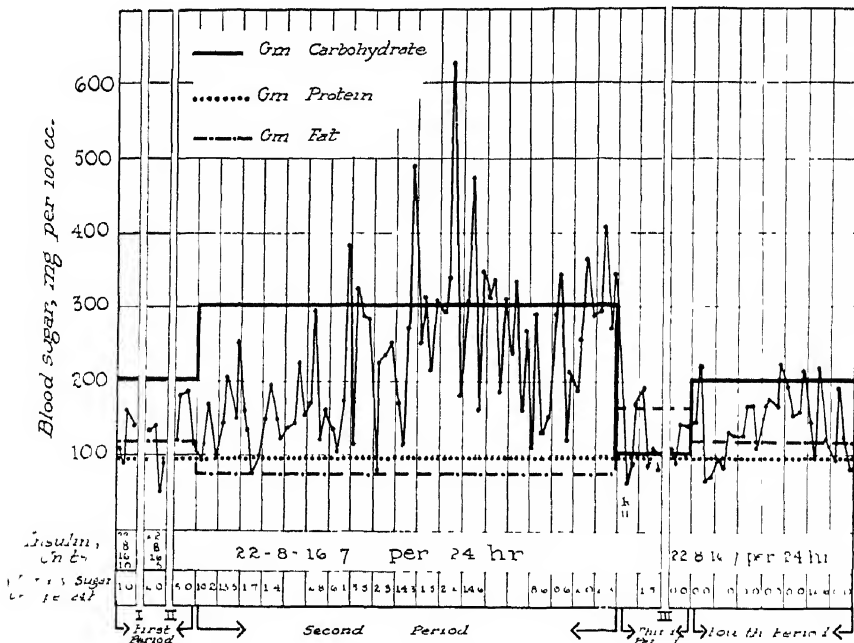


Fig 1—Curves showing the variations in the blood sugar level and the urinary excretion of sugar in relation to changes in the diet. The first period lasted 18 days. I indicates an interval of 10 days and II an interval of 5 days. III indicates an interval of 7 days. The fourth period lasted 7 days. The Roman numerals indicate intervals for which the data are omitted from the chart but for which they are essentially similar to those of the portions of periods shown (Am J Dis Child, March, 1938)

bohydrate, and the amount of insulin which would have been required to restore glycemic equilibrium probably would not have been great

The authors do not interpret the results of this observation as an argument for the use of free or unrestricted diets in the treatment of diabetes mellitus in children, but believe that it adds further support to the theory that a more normal type of diet may be used. The following factors appear to be of sufficient importance to justify the continued use

Hepatomegaly- Success in the treatment of hepatomegaly in juvenile diabetes mellitus with a pancreatic extract after failure to reduce the size of the liver with insulin and diet is reported by H. G. Grayzel and L. S. Radwin³⁴ Three diabetic children who had had extensive enlargement of the liver for a number of years were treated with a **pancreatic extract** prepared according to the method of L. R. Dragstedt, J. Van Prohaska and H. P. Harms³⁵ All previous efforts to cause a reduction in the size of their

livers had been unsuccessful. At first the pancreatic extract was administered in saline solution. Because it was not palatable in this form and its ingestion caused nausea, it was discontinued. It was subsequently desiccated and administered in salol-coated capsules. When the extract was taken regularly, the liver was reduced to normal within 3 to 5 months. Upon discontinuing the medication the enlargement of the liver recurred in 1 to 2 months. In each instance the decrease in the size of the liver was accompanied by a significant lowering of the total serum lipids and lipid phosphorus.

Prognosis—On the basis of data collected over a period of 10 years, J. D. Boyd and A. H. Kantrow³⁶ state that the well-controlled diabetic child may be expected to grow at a rate which equals or exceeds that of superior children. In their group of 167 children with diabetes mellitus, there were 10 whose stature or rate of growth over long periods was markedly lower than the standard values used for comparison. The determining factor in at least 5 of these cases was an insufficient intake of food. This probably played a large part in 3 other cases. In the other 2 cases it was impossible to determine whether the arrest of growth was dependent on therapeutic limitations

of the intake of food during the long period of absence from the clinic or on the associated, prolonged glycosuria. They conclude that if diabetes mellitus in children is suitably controlled through adequate diet and through avoidance of frequent or continuous glycosuria, retardation of growth will be prevented or corrected. Physical retardation should be considered a result of nutritional or allied metabolic inadequacies rather than a consequence of endocrine disturbances unless prolonged observance of an ample dietary regimen has failed to maintain a normal rate of growth.

The effects of insulin hypoglycemia upon the heart of diabetic children has been studied by H. F. Root.³⁷ From electrocardiographic and other clinical studies, the author concludes that insulin hypoglycemia has no serious effects upon the normal diabetic heart. Bradycardia was observed as frequently as tachycardia. It is stated that insulin hypoglycemia may, by reason of its accompanying stimulation of adrenal secretion, have serious effects upon the heart damaged by coronary disease. An instance of death resulting from overdosage of insulin was reported. It is suggested that insulin hypoglycemia of sufficient duration will cause irreversible changes in the central nervous system and death

DIGESTIVE SYSTEM

By WALDO E. NELSON, M.D.

Allergy

J. H. Fries and J. Zizmor³⁸ suggest that roentgenologic examination of the gastroenteric tract may provide additional information in the diagnosis of alimentary disturbances due to food allergy. They found that peristaltic disturbances in various parts of the gastro-

enteric tract followed the feeding of allergenic foods to allergic children and could be visualized roentgenographically. Apparently these disturbances may manifest themselves either by increased or decreased motility of the gastroenteric tract and by spasm (Fig. 2) or dilatation (Fig. 3) of the stomach or in-

TABLE I

SUMMARY OF ALL CASES BY YEAR WITH DIVISION OF CASES ACCORDING TO DIAGNOSIS AND TREATMENT—THE MORTALITY IS SHOWN IN EACH GROUP

Year	Acute Appendicitis Immediate Appendectomy	Deaths	Appendiceal Peritonitis Conservative Treatment	Deaths	Patients Treated Conservatively Deferred Appendectomy	Patients Treated Conservatively Failure to Return	Per Cent Treated Conservatively
1934	50	1	32	2	29	1	39
1935	36	0	29	2	25	2	45
1936	34	0	34	1	30	3*	50
1937	11	0	15	0	10	5*	57
Total	131	1	110	5	94	3 — — — 8*	45

* Cases which have appointments to return for interval appendectomy (J. Pediat., March, 1938)

testine. Subjective complaints referable to the gastroenteric tract usually accompany the objective findings.

Appendicitis

A mortality of 5.8 per cent is reported by P. D. Allen³⁹ in a series of 612 cases of acute appendicitis in children treated in the Children's Surgical Service at Bellevue Hospital over a 10-year period. This compares with the mortality rate of 7.58 per cent reported in 1924 from the same clinic. The younger the child and the longer the preoperative illness, the higher was the mortality. The relatively high death rate in the infants was due to the frequency of spreading peritonitis. The infant's lack of resistance to infection and the lack of sufficient omentum to wall off the process makes early operation necessary if one is to prevent spreading peritonitis with the resulting high mortality. While vomiting is usually the first symptom reported, it is likely that in most instances the child had previously suffered pain. The frequent use of cathartics administered by the mother and even by the family physician undoubtedly increases

and hastens the disease. In cases in which drainage is expected to be profuse, the author recommends suturing only the peritoneum in order to prevent sloughing of the fascia and muscles of the abdominal wall. This provides more adequate drainage and decreases the incidence of hernia. It is accepted that the peritoneum will stand greater contamination than the abdominal wall and that the abdominal wall in children is less resistant to contamination than that of the adult. The author recommends that when only the peritoneum is closed, interrupted sutures should be employed and care should be taken to include the transversalis fascia.

An unusual degree of success in the treatment of appendiceal peritonitis in children by conservative methods is reported by J. M. Adams and P. M. Bancroft.⁴⁰ The essential factor in their plan of treatment is the maintenance of complete rest, both general and of the gastroenteric tract. The latter is secured by means of continuous gastroduodenal syphonage by the Wangenstein method. The gastroenteric tract is almost completely relieved of activity by the con-



Fig 2 (Case 2)—*A*, Barium enema study made without the allergen, showing normal filling of the colon. *B*, Study made with the allergen (egg), showing spasm of the descending colon (Fries-Zizmor Am J Dis Child, Dec, 1937.)



Fig 3 (Case 3)—*A*, barium enema study made without the allergen showing normal filling of the colon. *B*, Study made with the allergen (milk), showing generalized distention of the colon. (Am J Dis. Child, Dec., 1937.)

tinuous removal of gas and fluids secreted by the stomach and intestine as well as such accessory excretions as bile and pancreatic juice. A diagram of the syphonage system is shown in Figure 4. At the onset the upper bottle

The child is placed flat in bed rather than in the semi-Fowler's position. The patient is allowed to swallow water while the tube is being passed. Small amounts of clear fluid are allowed, if desired, by mouth since they are immediately with-

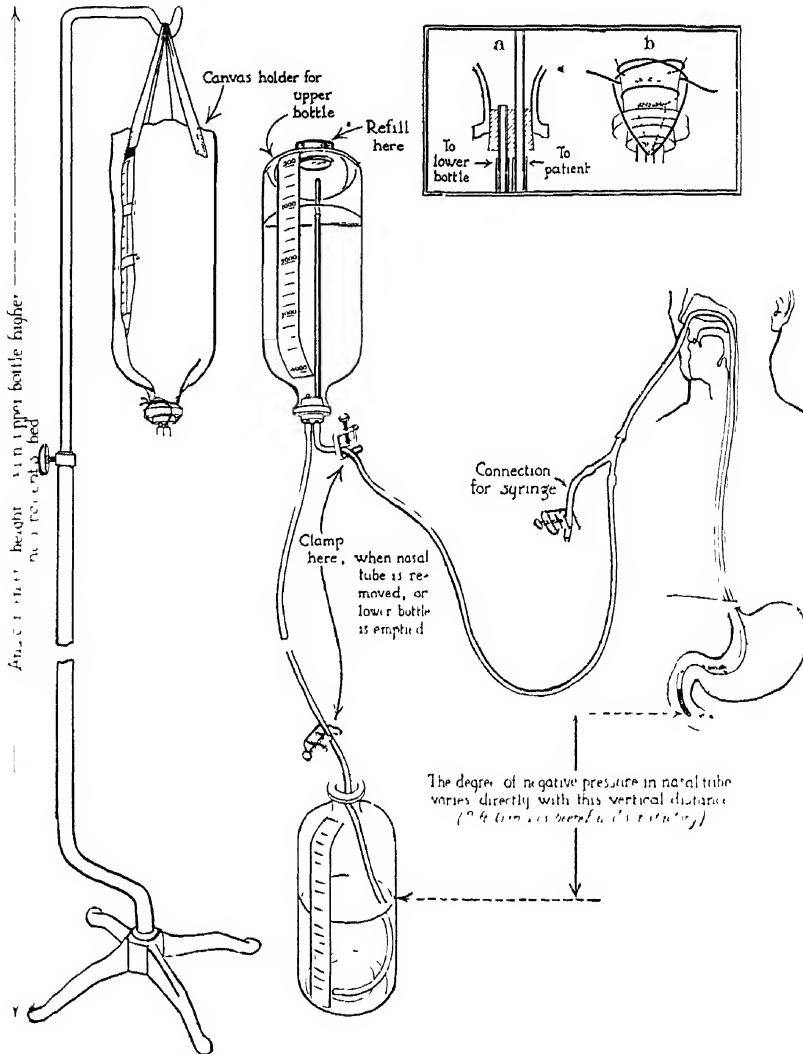


Fig. 4—A diagram of the gastroduodenal syphonage apparatus used in nearly all the cases of appendiceal peritonitis (J. Pediat., March, 1938.)

is filled with water except for 400 cc and the lower bottle is empty except for 400 cc to cover the tube. The amount of gas taken off is read directly on the scale on the upper bottle, and the amount of fluid removed is shown on the lower bottle.

drawn by the tube. The patient is kept on the right side and the tube passed 2 or 3 inches every 2 or 3 hours for the first 12 hours in order to facilitate the passage into the duodenum.

Hot applications are applied to the abdomen in the form of stupes. Sedatives

are administered for the control of activity, pain, and in order to depress the respiratory rate slightly. Fluids are administered by vein and hypodermoclysis. No fluids are given by rectum and no enemas are given. The unusual degree of success which the authors have had with this plan of treatment is shown in Table I.

Diarrhea

Good results with banana therapy in diarrheal diseases of infants and chil-

Intravenous Needle Holder

A needle holder for continuous intravenous infusion designed to prevent displacement of the needle has been designed by R. Cohen.⁴² The appliance is illustrated in Figs. 5 and 6. The principle is a needle clip on a friction hinge attached to a U bar. After the needle or cannula is inserted into the vein, the U bar is slipped under the needle and moved forward until the clip is inserted on the hilt of the needle. It is then

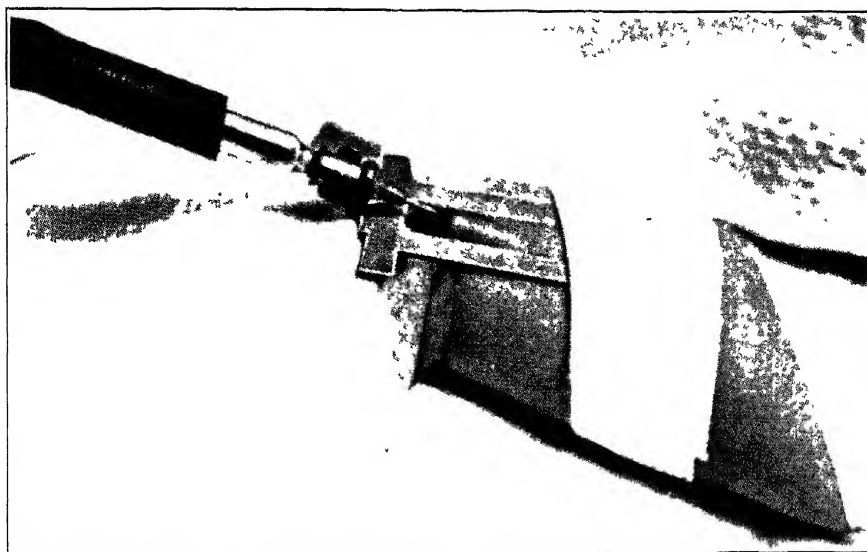


Fig 5
(J Pediat, April, 1938)

dren are reported by C L. Joslin, J. E. Bradley and T A Christensen⁴¹ Their series consisted of 65 infants and children of whom 43 were treated in the hospital and 22 in the outpatient dispensary. Their routine was as follows. During the first 24-hour period nothing was given by mouth except water. When necessary, parenteral fluids were administered. Following this initial period of starvation, banana, either in the form of the ripe fruit or as a dehydrated powder, was introduced into the diet in either skimmed milk or buttermilk.

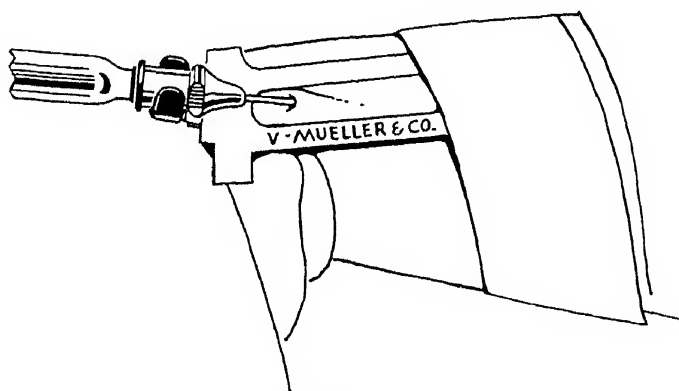
angulated to the desired degree. The front of the parallel bars is taped to the skin, and the base wings taped if desired.

Pyloric Stenosis

E J Donovan⁴³ reports the successful surgical treatment of 143 consecutive cases of congenital hypertrophic pyloric stenosis. Since he has had little success with the various forms of medical treatment, such as the administration of atropine, thick feeding or refeeding after vomiting, he advocates surgical intervention as soon as the diagnosis is estab-

lished, except in mild cases when the infants are nearly 3 months of age. He argues that medical treatment, at best, is prolonged and uncertain and requires expert nursing care, long hospitalization and removal of the baby from the breast. Surgical treatment, on the other hand, is quick, certain and permanent in its results and permits breast feeding to be resumed a few days after operation. Pre-operative preparations is said to be the most important factor in lowering the operative mortality. It is not necessary

30 cc. per feeding at the end of 48 hours. The breast milk per feeding is then increased from 5 to 10 cc. daily until the caloric requirements are met. One or two infusions of physiologic solutions of sodium chloride or 3 per cent dextrose in salt solution are given each day for 3 days. All feedings for the first 5 days are given with a medicine dropper and the babies are allowed to nurse once on the fifth day, twice on the sixth day and so on until they are completely breast fed.



No. 6
(J. Pediat., April, 1938)

to operate in the severe cases as an emergency measure. In such instances, the infant should be given 1 or 2 preoperative **transfusions** of whole blood, allowing 20 cc. per kg. of body weight. Since most of these infants have alkalosis, with a high concentration of serum carbon dioxide and a low concentration of blood chloride, they are given from 1 to 4 transfusions of 100 cc. of **physiologic solution of sodium chloride** before operation. Two hours after operation, 15 cc. of water are given by mouth and 4 hours later, the first feeding, consisting of 4 cc. of breast milk and 4 cc. of barley water, is given. The breast milk and barley water are increased from 5 to 10 cc. with each 3-hour feeding until the infant is taking

Stomatitis

Evidence that the virus of herpes simplex is the causative agent of lesions in the oral cavity ordinarily described as aphthous stomatitis is presented by K. Dodd, L. M. Johnston and G. J. Buddingh.⁴⁴ Although children are rarely seen in the early stages of the disease, the authors, on the basis of histories and 1 or 2 cases seen early, believe that the onset is sudden with fever, general malaise and loss of appetite. Either with the onset of fever, or 24 hours or more later, lesions appear in the mouth. During the early stages, they consist of reddish blisters on the mucous membrane. Soon the blisters became ulcerated and the ulcers covered by a yellowish white membrane. The commonest sites

of the lesions are the tongue, the inner surface of the lips and the buccal and sublingual mucous membrane. More rarely they occur on the outer mucous membrane of the lips, the soft palate, tonsils and posterior pharynx and very occasionally in the larynx. In every in-

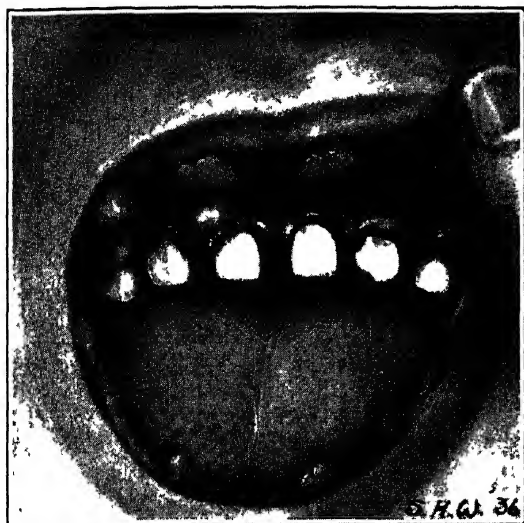


Fig 7—Mouth lesions in a typical case of herpetic stomatitis (J. Pediat., Jan., 1938)

stance there are, besides the local lesions, marked redness and swelling of the gums with a tendency to bleed easily. Salivation is greatly increased. Figure 7 illustrates the mouth lesions in a typical case.

In 12 of the cases, inoculation of material from the lesions was made into the cornea of rabbits. In each instance

a purulent, keratoconjunctivitis typical of herpes simplex was produced. In 9 of the 12 rabbits typical intranuclear herpetic inclusions were present in the infected cornea. Immunity to a known strain of herpes simplex was demonstrated in 6 of 7 rabbits which survived the infection. The authors believe that the stomatitis described is a definite clinical entity and should be designated as herpetic stomatitis. Since most cases of herpetic stomatitis occur in children, it is probable that the disease represents a primary herpetic infection.

Vomiting

Recently interest has been stimulated in the problem of ketonemia in infancy and its relation to vomiting. Data concerning the blood ketone values of healthy infants and infants with vomiting have been collected by C. H. Gray.⁴⁵ The blood ketone value of healthy infants varied from 1.4 to 2.0 mg. per 100 cc. of whole blood. Vomiting infants under 3 months of age showed slightly higher values with variations from 1.6 to 4.5 mg. per 100 cc. Vomiting infants over 3 months of age had much higher values, from 2 to 19 mg. per 100 cc. Seventy per cent of them had values higher than 4.5 mg. The same age difference was noted in the incidence of severe fatty changes in the livers of 108 children who died of diseases associated with vomiting with and without diarrhea.

DIPHTHERIA

By ROBERT A. LYON, M.D.

Epidemiology—The annual report of *diphtheria mortality* in the large cities of the United States during the year 1937 has demonstrated a continuation of the downward trend which has been in prog-

ress for the past decade.⁴⁶ The cities of the middle Atlantic states had the lowest death rates for both 1936 and 1937. Close contenders for this record were the cities of the New England states. In several

of the cities of these 2 groups there were no deaths from diphtheria in 1937 and when the deaths among non-residents were excluded from the figures, the number of cities with perfect records was even greater. In the south Atlantic cities the general rate declined but there was no city without a death. In the east-north-central states, a group of cities had an increase in the number of deaths from 168 in 1936 to 186 in 1937. In the south-central states, the rate increased during the past year and all but one of the cities had more than 3 deaths per 100,000 population. The cities in Texas, Oklahoma and Louisiana, had the highest mortality from diphtheria in the country but there was a general decline in the rate during the past year. In the other western cities there was also a general decline in death rate. Throughout the entire country there were 20 cities with no deaths from diphtheria and there were but 3 cities with death rates over 5 per 100,000. The general decline of mortality in 1937 was indicated by the rate of 1.46 as compared with 1.51 for the previous year of 1936. The total number of diphtheria deaths, however, declined by only 9, from a total of 577 to 568 in 93 cities. (See tables.)

The marked decline in morbidity and mortality rates of diphtheria in Canada has been attributed definitely to the general employment of immunization methods by J. G. Fitzgerald, D. T. Fraser, N. E. McKinnon and M. A. Ross.⁴⁷ Before the year 1925, the widespread use of antitoxin in the treatment of diphtheria had little effect in reducing the rates of incidence or death from the disease but since that year toxoid materials have been distributed widely with marked effects on both rates. In the province of Ontario, for example, morbidity rates fell from 97 per 100,000 population in the year 1930 to 10 per

100,000 in 1934 and the mortality rates fell from 6.0 to 0.6 in the same years. Several problems remain to be solved, such as the revision and standardization of the Schick test, a better understanding of the interpretation of the Schick reactions, a selection of the best immunizing material and more extensive use of measurements of blood antitoxin as standards for the selection of immunizing agents and test material.

From a review of the morbidity and mortality statistics of diphtheria in Vienna during the past few decades, V. Gegenbauer⁴⁸ concluded that diphtheria occurred with greatest frequency in younger children during the years before the World War, but recently the incidence among children of school age is as great as it is in the younger patients. A similar trend was noted in respect to scarlet fever. Slight increases in the total number of patients suffering from both infections have occurred during the past few years.

Bacteriology Variations in the toxic properties of diphtheria bacilli, classified generally as *gravis*, *mitis* and

TABLE I
TOTAL DIPHTHERIA DEATH RATES FOR
88 CITIES, 1923-1937

	Population	Diphtheria Deaths	Diphtheria Death Rate per 100,000 of Population
1923	31,060,848	4,078	13.13
1924	31,722,841	3,439	10.84
1925	32,384,834	3,133	9.67
1926	33,046,827	3,106	9.40
1927	33,708,820	3,493	10.36
1928	34,370,813	3,176	9.24
1929	35,032,806	2,738	7.82
1930	35,694,802	1,827	5.12
1931	36,503,412	1,366	3.74
1932	37,084,712	1,191	3.21
1933	37,084,712	861	2.32
1934	36,777,112	821	2.23
1935	36,777,112	764	2.08
1936	37,575,105	561	1.50
1937	38,169,704	556	1.46

TOTAL DIPHTHERIA DEATH RATES PER HUNDRED THOUSAND OF POPULATION FOR
93 CITIES ACCORDING TO GEOGRAPHICAL DIVISIONS

	Population	Diphtheria Deaths		Diphtheria Death Rates			
		1937	1936	1937	1936	1930-1934	1925-1929
New England	2,640,933	21	28	0.79	1.06	3.38	8.34
Middle Atlantic	13,426,805	95	87	0.71	0.65	2.50	9.97
South Atlantic	2,609,531	53	67	2.04	2.59	3.54	7.37
East North Central	9,870,249	186	168	1.88	1.73	3.66	11.21
East South Central	1,330,969	42	38	3.16	2.96	6.36	6.34
West North Central	2,778,245	35	38	1.26	1.37	3.22	7.82
West South Central	2,084,616	67	87	3.21	4.39	6.55	9.24
Mountain and Pacific	4,144,087	59	71	1.43	1.78	2.69	6.28

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intermediate forms have been detected in many localities. In a study of 91 patients with diphtheria and of 10 carriers of the disease in Moscow, S. L. Shapiro and M. V. Rukevitch⁴⁹ found mitis types of diphtheria bacilli in 63 per cent of the group, intermediate types in 28 per cent, gravis types in 6 per cent and atypical forms in 3 per cent. There seemed to be no definite relationship between severe clinical forms of the disease and the occurrence of gravis types of bacilli, but during periods in which diphtheria was not epidemic and the cases were generally mild, the forms of bacilli were generally of the mitis variety. When epidemics were more severe the gravis types were isolated with greater frequency.

Clinical manifestations and complications—Two unusual clinical forms of diphtheria have been reported by E. F. Dawson-Walker and E. G. Brewis.⁵⁰ The first was a mild nasopharyngeal diphtheria in an infant, 2 weeks of age, who also had a septic omphalitis and an ulceration of the right groin. The mother was found to be a carrier of the disease. Diphtheria under 1 year of age is rare, occurring only 8 times, or in 0.64 per cent, of a series of 1250 consecutive cases observed by the authors. Figures

from other clinics give an incidence in this age group as 0.15 per cent to 2.0 per cent. Mortality rates are apt to be high in these young patients.

Another patient, a boy 12 years of age, had a severe diphtheritic infection followed by paralysis of the pharyngeal muscles and evidence of myocarditis. Two months later, he developed *choreiform movements* with emotional instability. Slow but complete recovery occurred during the next 3 months. No previous symptoms of chorea or other rheumatic infection had been noted in this boy and it was believed that the diphtheria toxin had invaded the basal nuclei and other portions of the brain. Only 2 previous reports of postdiphtheritic chorea were found by the authors.

The development of diphtheritic *skin lesions* in a child with a double infection of scarlet fever and diphtheria was noted by J. T. MacCarthy.⁵¹ The eruption was a mild, moist dermatitis behind the ear and in the axilla and cleared readily after the administration of diphtheria antitoxin and the local applications of a mercurial ointment. The author raised the question whether many innocuous lesions of the skin might not be invaded by the diphtheria bacillus and

such infections might contribute to the immunity gained by many individuals without suffering from other severe manifestations of the disease.

The effect of diphtheria toxin on the heart has been observed in a series of experiments by D. B. Witt, E. Lindner and L. N. Katz.⁵² Determinations were made in a series of 18 dogs of the heart rate, rhythm, arterial and venous pressures, systolic, diastolic and pulse pressures, diastolic and stroke volume, minute volume flow and changes in the cardiac muscle tone and conduction. The diphtheria toxin first caused a sinus slowing of the heart rate and then various types of conductive block, extrasystoles and paroxysmal tachycardia. Ventricular fibrillation was a frequent terminal phase. The systemic and pulmonary blood vessels dilated with a consequent diminution of blood supplied to the heart by the coronary arteries. The toxin, however, seemed to cause direct myocardial damage before the vasodilatation was a prominent symptom and the myocarditis may, therefore, be present before the electrocardiogram or blood pressure determinations indicate any abnormality.

The *electrocardiographic changes* occurring in the course of toxic diphtheritic infections have been reviewed by E. A. Burkhardt, C. Eggleston and L. W. Smith.⁵³ Of a total number of 140 patients with the infection, only 28 showed evidence of cardiac damage. Twenty-three patients had abnormalities of the T-wave, occurring on the fifth to the thirty-ninth day of the illness. The changes began with a decline of the level of the S-T line and a decrease in amplitude of the T-wave. The T-wave became smaller in amplitude until it was isoelectric, diphasic or inverted. Death occurred in 3 such patients. Conduction changes, which occurred in 17

patients, consisted of ventricular escape, prolonged QRS intervals, intraventricular block and auriculoventricular dissociation. These lesions developed on the fifth to thirteenth day of the diphtheria and were more frequent in younger age groups of patients. Those with A-V dissociation died. At autopsy, the general sequence of the cardiac involvement seemed to be edema, congestion, cellular infiltration, degenerative changes and finally fibrosis. The electrocardiogram seemed to be a valuable adjunct to the diagnosis of the extent of cardiac damage in these patients.

An unusual complication of diphtheria, consisting of occlusion of the abdominal aorta, was observed in a patient, 10 years of age, by D. Bobeff.⁵⁴ Symptoms of pain and cyanosis in the lower extremities occurred on the sixteenth day after the onset of the diphtheria and within a short time ulcerations developed on the feet, and the toes became gangrenous. Death occurred in 3 days. At autopsy, a thrombosis of the abdominal aorta was found, together with infarcts of the kidney, parenchymatous degeneration of the myocardium, liver and kidney.

Treatment Laryngeal diphtheria is usually treated by *intubation*, *tracheotomy* or by *aspiration of the trachea*. The first method has been preferred by A. G. Robb.⁵⁵ In a series of 951 patients, intubation was followed by a mortality rate of 24.7 per cent. An additional group of 61 patients required tracheotomy following attempts at intubation and the mortality rate in this series was 60.6 per cent. The necessity for tracheotomy arose because of (a) the small size of the trachea in young patients for which tubes of the proper caliber were not available, (b) edema of the trachea which prevented satisfactory intubation, (c) poorly fitting tubes,

or finally (*d*) the absence of a trained clinician to insert the tube. Suction methods of treating laryngeal diphtheria were adequate in only a small number of cases. Tracheotomy, which is preferred by some clinicians, frequently resulted in higher mortality rates, according to the reports from other institutions, sometimes reaching as high as 60 per cent in large series of patients. The author was inclined to believe that intubation was the safer method of treatment and that only a small amount of training was necessary for one to employ it with safety.

Tracheotomy has been the operation of choice in the treatment of laryngeal diphtheria by W. Napier.⁵⁶ Over a period of 11 years, laryngeal involvement occurred in 220 patients of a total series of 2528 patients with diphtheria, an incidence of 8.7 per cent. Of this group, 55 required operation and 44 made good recoveries. The tracheotomy tube could usually be removed within a few days after insertion although children under 4 years of age sometimes developed laryngeal spasm when the tube was withdrawn. The group of 14 patients who died seemed to have improved temporarily following tracheotomy except in 1 instance. Bronchopneumonia occurred in 4 instances and toxemia seemed to have been responsible for the deaths of the other patients. A follow-up study of 19 patients indicated that no serious difficulties which might be attributed to the tracheotomy had developed in later years. Bronchitis and huskiness of voice occurred in a few instances and tuberculosis caused the death of 1 child but the part played by tracheotomy in this case was doubtful. In the general review of mortality rates from tracheotomy, it was noted that the figures varied from zero to 18.7 per cent in different years but when the entire experience of 11

years was taken into consideration, the rate was only 6.8 per cent for the 55 patients. These rates compared very favorably with mortality statistics of groups in which intubation methods were practiced.

A comparison of intubation and tracheotomy as methods of treatment of obstructive laryngitis has been made by W. A. Howard.⁵⁷ His series of patients included 29 cases of diphtheria and 34 patients with laryngitis of other types. Most of the children were less than 5 years of age. *Intubation* was employed alone in 40 instances, *tracheotomy* in only 5 patients and both procedures in 18. All of the children treated with tracheotomy died and the mortality in the other groups was 38 to 42 per cent. In the diphtheria patients, intubation was the treatment of choice and tracheotomy was employed when the former method failed. Intubation of nondiphtheritic patients, whose laryngitis was caused principally by forms of streptococci and staphylococci, was less successful than in the diphtheritic group. Eleven of a series of 17 such patients died. The author concluded, however, that intubation was the treatment of choice in all cases of laryngitis.

The relationship of *vitamin C* to diphtheria has been studied from various aspects during the past year. Treatment of severe diphtheria with vitamin C has given good results in Osaka, Japan, according to the report of K. Kumagai, S. Yamagami, Y. Nikai and S. Imai.⁵⁸ The average mortality rates of diphtheria in this locality had been 13 to 17 per cent, and many of these infections were of the necrotic type. Large doses of antitoxin and glucose solutions had had no influence in reducing the mortality rate. Since the year 1935, large amounts of vitamin C (400 to 600 Gm. daily) administered to diphtheria patients with

severe forms of the disease has been attended by great improvement of their general condition. The heart rates became more regular, urinary output increased and the mortality rates decreased to approximately one-half of their former levels. The high levels of blood sugar which occurred in several patients with severe diphtheria who subsequently recovered, dropped rapidly when vitamin C was administered. In fatal cases the blood sugar levels did not decline and the authors concluded that the vitamin exerts its beneficial action through the regulation of sugar metabolism.

The addition of ascorbic acid to the culture media of diphtheria bacilli retarded the toxin production in experiments conducted by I. J. Kligler, L. Leibowitz and M. Berman.⁵⁹ Concentrations of vitamin C of 0.05 to 0.1 mg. per cc. of the media reduced the toxicity of the filtrate to one twentieth of that produced in control tubes. The action occurred under aerobic and anaerobic conditions and was most effective at temperatures of 86° to 98.6° F. (30 to 37° C.). Another oxidation-reduction agent, glutathione, had no action similar to the vitamin, and the authors concluded that the ascorbic acid had a direct effect upon diphtheria toxin similar to that produced by certain aldehydes.

No beneficial effects from ascorbic acid in the protection of guinea pigs from diphtheria toxin could be observed by S. S. Zilva.⁶⁰ When the vitamin was injected just before or after administration of the diphtheria toxin and when the tissue content of ascorbic acid was high, the guinea pigs succumbed to the toxin injections as readily as did those who had been given scurvy-producing diets and consequently had very small amounts of the vitamin in their blood and tissues.

In a study of the effect of vitamin C on diphtheria toxin, J. Pakter and B. Schick⁶¹ employed the Schick reaction in human patients as a method of evaluation. When vitamin C was administered orally and intravenously to a series of patients, no appreciable reduction in size of the Schick reaction took place. The local subcutaneous injection of cevitic acid likewise had no effect in reducing the size of the reaction to the Schick test material injected later at the same site. When the Schick tests were repeated at frequent intervals after the administration of vitamin C, a slight decrease in size of the test occurred within 2 to 3 hours only. It was suggested that the results of *in vitro* experiments in which vitamin C seemed to neutralize diphtheria toxin, may have been due to certain nonspecific factors such as a marked reduction reaction or an alteration of the pH of the mixture.

Serum reactions following the treatment of diphtheria patients with **antitoxin** have been noted less frequently since the serum has been concentrated by the removal of excess protein material. A review of this subject by H. M. Davis⁶² included the results obtained in a group of 4835 patients who had received the concentrated diphtheria serum. Approximately 22 per cent of this series had some form of serum reaction which was a considerably lower incidence than the 40 to 66 per cent reported previously in patients treated with whole, untreated serum. In the author's series, serum reactions occurred most frequently in children under 5 years of age and the incidence of reactions seemed to be increased by such factors as large doses, induced sensitivity by previous injections and variations of potency of different sera. Skin rashes, usually of urticarial, scarlatinal or morbilliform types, were the most frequent manifestations of

serum reactions and they developed most frequently on the eighth day after administration of serum. Other lesions were edema of the hands or feet, joint pains, albuminuria and fever.

Immunization—The value of active immunization against diphtheria has been demonstrated in the analysis of the incidence and mortality rates of that disease over a period of 6 years by A. G. Morrison and L. Roberts.⁶³ During this period of time 3924 cases of clinical diphtheria developed in a total child population (aged 0 to 15 years) of 91,625. Immunization against diphtheria had been carried out in 18,800 children and more than 10,000 of these patients were known to have been Schick negative after the treatment. Clinical diphtheria developed in 146 of the total number of children who had received immunizing injections and in 40 of those who had had negative Schick reactions. Only 2 deaths occurred in the treated group and none in children known to have had negative skin tests. Analysis of these figures indicated that the chances that a treated child would contract diphtheria were less than a third as great as those of an untreated patient and if his Schick reaction was made negative, his chances were less than a sixth of those of an untreated patient.

The statistical analysis of the results of immunization of 5195 children with plain toxoid over a period of about 8 years has been reported by B. Benjamin, G. Fleming and M. A. Ross.⁶⁴ Within 6 to 11 months after the 3 inoculations of toxoid, approximately 96 per cent of each age group had negative Schick reactions. As the time interval between the last dose of toxoid and the Schick test was prolonged to 2 years or more, the percentage of negative skin reactions decreased. Three doses of toxoid produced a more lasting immunity than did only 2 doses and the intervals of time

which elapsed between the administration of the 2 or 3 doses seemed to make very little difference in the final results obtained.

With a single injection of alum precipitated toxoid, a high percentage of negative Schick reactions were obtained by H. W. Straus.⁶⁵ A group of 63 susceptible children were treated in this manner and approximately 90 per cent of the 43 children who were retested 11 to 27 months later had negative Schick reactions.

The *duration of diphtheritic immunity* which has been produced by various artificial methods has never been adequately studied from an accurate statistical viewpoint. This was the recent statement of W. H. Park,⁶⁶ who has reviewed some of the recent experiments in this field. In animals, the injection of 1 dose of alum precipitated toxoid followed by a single dose of fluid toxoid has produced the greatest and most lasting immunity while 2 or 3 doses of the unmodified toxoid gave the poorest results. In children, 3 doses of toxin-antitoxin or a single dose of alum precipitated toxoid produced a higher percentage of negative Schick reactions than did 2 doses of unmodified toxoid. A third experiment quoted by the author indicated that 3 doses of toxin-antitoxin or 2 doses of unmodified toxoid produced a more permanent immunity than could be obtained with the injection of 1 dose of alum precipitated toxoid. In all of these experiments the author concluded that the number of children was too small to be of statistical significance and in the future such experiments should be adequately controlled. The various immunizing agents of comparable potency should be administered in similar dosage and the experiments should be conducted over a period of 5 years or more. It was his conclusion that the

data now available are not adequate for statistical analysis and that until more information is gathered in regard to the best method of immunization against diphtheria it is advisable to employ 2 or 3 doses of either the unmodified fluid or alum precipitated toxoid.

In order to judge and compare results obtained from immunization, standards of antitoxin response in children have been prepared by D. T. Fraser and K. C. Halpern.⁶⁷ Measuring the antitoxin content of the blood of 244 children after 3 injections of unmodified diphtheria toxoid material, they found that after a period of 3 months from the last injection, all but 1 child had amounts of antitoxin which were considered adequate for protection against the disease. In comparing this with the antitoxin levels of children who had acquired their immunity spontaneously, they observed that the amount of protection obtained in this manner was less than that produced by artificial immunization. When children were tested 6, 9, 12, 18, 24 and 36 months after having received the toxoid injections, it was found that the antitoxin levels in the blood tended to decrease slowly. There was a drop in blood antitoxin levels of approximately 50 per cent in the group as a whole over a period of 1 year and then a slow decline during the next two years until an average of only 34 per cent of antitoxin remained. Antitoxin, resulting from natural stimuli, seemed to persist at higher levels over a longer period of time. The authors have suggested that standard tables of antitoxin levels and the rate of disappearance of antitoxin be employed in the comparison of effects of all antigens employed in the immunization against diphtheria. In a number of patients too small to give results of statistical significance, they have compared the antigen response obtained with

toxoid materials given in various dosage. The administration of 2 doses of alum precipitated toxoid was the only procedure which gave results comparable in effectiveness with those obtained with 3 injections of unmodified toxoid.

Immunization against diphtheria by a combined *subcutaneous and intranasal method* has been suggested by C. Jensen.⁶⁸ With a single injection of a purified alum toxoid, the antigenic response of the patient, judged from blood antitoxin determinations, was found to begin in 10 to 21 days and in some cases to reach its maximum in 3 weeks and continue for 3 to 5 weeks. About 95 per cent of various age groups responded to the stimulus of this alum toxoid injection. Reactions occurred more frequently in children who had had diphtheria previously (43 per cent) than in those with no history of the disease (178 per cent). Young adults had reactions in even greater percentages. For intranasal instillation, use was made of a highly purified formal toxoid, which was isotonic and buffered to a pH of 7.3. No reactions or unpleasant sensations occurred when the material was instilled into the nose. In both animal and human experiments the nasal instillation of toxoid enhanced the immune response. The intranasal method alone did not always produce an adequate antitoxin response but the author recommended its use in conjunction with the one injection method of immunization. By such a combination, the number of injections could be reduced to 1. The nasal instillations given in 3 doses would increase the antitoxin response and might be used at the beginning of each winter or in the presence of an epidemic of the disease to raise the blood antitoxin to proper levels for immunity.

The production of diphtheria immunization by *inhalation* of toxoid vapor has

been tried by G. Bousfield and W. W. King-Brown.⁶⁹ Instead of direct application of toxoid to the nasal mucous membranes, an atmosphere of toxoid in a room of about 1800 cubic feet was produced by spray which atomized 50 cc. of toxoid material. Six adults were exposed in this room on 2 occasions for periods of 50 minutes each. One other patient, who developed allergic manifestations after 1 treatment, was excluded from the series. Four individuals had rather severe reactions following the treatment, their symptoms consisting of chilliness, cough, headache, tightness of the chest, joint pains and vomiting. The patients with such reactions, however, developed large quantities of antitoxin in their blood with the levels rising from one-tenth to as high as 5 and 10 units per cc. The patients with no reactions showed less antitoxic response. It seemed possible that the dosage might have been too high, or that younger patients with less sensitivity to the material might profit more by such an immunization procedure.

Severe reactions in patients receiving the immunization treatment has caused some criticism of the procedure employed. Many of these reactions might be prevented if the sensitivity of a patient is determined by an initial skin test with the immunizing agent. This is the so-called Moloney test, whereby 0.2 cc. of the toxoid, diluted 1:20, is injected intradermally.

H. A. Raeburn⁷⁰ has found that patients with positive Moloney tests rarely have severe Schick reactions. One might conclude that a patient who is sensitive to formalized toxoid has a moderate degree of immunity, and, conversely, the patients who have the greatest need for immunization are less apt to be sensitive to the injected material. When sensitivity is detected in a patient requiring

immunization, the author has found that other materials such as toxoid-antitoxin mixtures of floccules may be employed with safety. The toxoid-antitoxin mixtures, however, contain horse serum and it has been demonstrated that they may induce a sensitivity in patients to all future horse serum therapy. Three unusual types of reactions to immunization treatment which the author has observed were scarlatinal rashes, petechiae and herpes labialis.

Combined Diphtheria and Tetanus Immunization—Since tetanus toxoid has proved to be an effective immunizing agent, consideration has been given to the combination of it with diphtheria toxoid for the active immunization of children against the 2 diseases simultaneously. F. G. Jones and J. M. Moss⁷¹ administered 2 doses of a combined alum precipitated toxoid to a group of 41 medical students who were susceptible to diphtheria. Severe local and general reactions occurred in 12 per cent of the group after the first injection and in 7 per cent after the second. The dosage of the second inoculation had been reduced to one-half in 6 patients because of the severity of the initial reaction. In general, the reactions to the combined toxoids seemed greater than usually observed with the use of diphtheria toxoid alone. All of the group developed adequate immunity to both diseases as measured by the skin reaction and the blood antitoxin content. Subsequent injections of either toxoid seemed to produce a rapid increase in the antitoxin content of the blood. The authors believed that the combined toxoid injections would be specially valuable for routine use in small children.

A plea for the use of *combined diphtheria and tetanus* immunization has been made by J. V. Cooke.⁷² The mortality rate from diphtheria is about 15 per

100,000 population and the deaths from tetanus are only slightly fewer, 1.1 per 100,000 population. More than half of the deaths from tetanus occur in children less than 15 years of age. The combined alum precipitated toxoids seemed to give no more severe reactions than the toxoid of diphtheria alone and 2 doses of the combined material will build up adequate protective bodies against both diseases. This procedure has been adapted as a routine method in the author's clinic.

The Schick Test—Clinical diphtheria does not always confer immunity adequate to render Schick tests negative. A series of 87 patients recovering from the disease were skin tested 6 weeks or more after the infection, by F. Pygott⁷³ and 9 of the group had positive reactions. The age of the patient and the time at which antitoxin was administered in relation to the onset of the infection seemed to have no bearing on the incidence of the positive reactors. All but 1 of the patients who developed paralysis had negative reactions. There were 3 patients with positive Schick tests who harbored virulent diphtheria bacilli in their nose and throat secretions and yet had no clinical evidence of infection. Immunization of the Schick positive reactors by artificial methods was successful in every instance.

The accuracy of the Schick reaction in measuring the amount of antitoxin in the blood of an individual has been investigated recently by H. J. Parish and J. Wright.⁷⁴ In their observations

the levels of blood antitoxin were found to be generally higher in the Schick negative reactors but the test could not always be relied upon to give accurate information. Several individuals had negative reactions with very low amounts of antitoxin in the blood. Even when Schick material of 4 to 10 times the normal potency was employed some of the patients with small amounts of antitoxin did not give positive results. Since pseudoreactions with these more potent testing toxins were often severe, the authors could not recommend their general use. It seemed likely that many individuals who have low titers of antitoxin but are Schick negative probably respond rapidly with a production of immune bodies when they are infected with diphtheria bacilli. A few Schick-negative individuals who do not respond quickly or who experience attacks by the gravis forms of diphtheria bacilli may contract the illness. The conclusion was reached that an additional injection of a diphtheria immunizing agent would be beneficial for even the Schick negative child at certain periods of life, such as the age of entering school and again maybe when he was 9 years of age.

Schick reactions made negative by immunization reverted to positive within a period of 6 or 7 years in a group of 145 children observed by A. B. Schwartz and F. R. Janney.⁷⁵ They emphasized the necessity of repeating the Schick test in children when they reach school age, or of giving routinely another injection of the antigen at that age without testing their immunity.

ENDOCRINE DISTURBANCES

By JOSEF WARKANY, M.D.

Adrenals

The clinical, hematologic and pathologic data in a case of adrenal sympathicoblastoma (neuroblastoma) occurring in a male child, 2½ years old, are recorded by K. Kato and H. E. Wachter.⁷⁶ Smears made from materials aspirated from both the sternal marrow and a cervical lymph-node contained clusters of typical, slightly basophilic cells with relatively large hyperchromatic nuclei and fluid-like cytoplasm which as a rule was scant in amount. These cells, when later compared with the malignant cells, similarly demonstrated from the tumor masses, were identified as metastatic sympathicoblasts or neuroblasts from the primary focus in the adrenal glands. Identical cells and groups of cells, but often with 2 or 3 nuclei and of larger dimensions, were also found in the imprint preparations made from the cut surface of the metastatic nodule in the skull. No typical rosette formation of the pathologic cells was seen in any of the preparations studied. Instead, the ball-like aggregations of cells described more typically as mosaic patterns were seen. For this reason, the general configuration of cell clusters characterizing this type of neoplasm would be referred to as pseudorosettes or preferably mosaic. While the tumor, owing to the major localization in the skull, was properly classified as a Hutchinson type of neuroblastoma, there were also numerous metastatic nodules of tumor tissue in the liver, indicating that such a classification is purely arbitrary. The hematology of adrenal neuroblastoma and its differential diagnosis from chloroleukemia and lymphosarcoma with which the condition is most frequently confused are discussed in this paper.

I. McQuarrie, R. M. Johnson and M. R. Ziegler⁷⁷ made a study of the plasma electrolytes in the case of a patient presenting a persistent tendency toward alkalosis in addition to the clinical features characteristic of suprarenal cortical syndrome or Cushing's syndrome of pituitary basophilism. Disturbances in the electrolyte pattern of the plasma were in most respects diametrically opposite to those found in a typical case of Addison's disease.

The most striking abnormalities were the high concentrations of bicarbonate and sodium and the decrease in potassium and chloride. The plasma magnesium, calcium, inorganic phosphate, and protein were reduced to levels slightly below normal. Before insulin therapy was instituted, the organic acid plus sulfate fraction estimated by difference between total base and determined acid constituents was greatly increased in spite of the absence of ketonuria. This was completely reduced by insulin therapy. Neither cortin subcutaneously nor massive doses of sodium chloride by mouth caused a rise in the plasma chloride. A combination of the 2 was equally ineffective. Potassium chloride injection, on the other hand, caused both the chloride and the potassium to return to normal levels although the dosage was but one-fourth that of the sodium salt given previously. Coincidentally, the plasma bicarbonate was temporarily reduced to near the normal value.

It is perhaps the very exceptional case of interrenalism only that suffers from such a marked disturbance of the acid-base metabolism as that described. Because of the striking and almost complete contrast between Addison's disease which is so clearly due to hypofunction

of the adrenal cortex and the type of case presented here, the authors believe that the latter represents a true example of hyperfunction of the cortex and so might well be referred to by the designation "hypercorticoadrenalism" or the "hypercorticoadrenal syndrome." It appears likely that not a single hormone but several are involved in the production of this complex disorder.

Gonads

A case of *pubertas praecox* in a 4-year-old girl is described by E. Mannheimer.⁷⁸ Menstruation started at the age of 4 years and secondary sexual characters appeared at the same time. She also showed increased growth in length and early ossification of the bones. The etiology of this disturbance was found in a dextrolateral granulosa cell tumor of the ovary. The Aschheim-Zondek reaction was negative and the percentage of prolan in the urine of the patient was insignificant. It seems probable that the hormone excretion from the granulosa cell tumor in this case played an important rôle not only in the development of the secondary sexual characteristics but also in the rapid growth of the bones during that period. This belief is also proven to some extent by the fact that the development of the bones after the extirpation of the tumor at re-examination more than a year after the operation did not seem to have proceeded any further.

An experimental study of the effects of male hormone upon the descent of the testes was made by J. B. Hamilton.⁷⁹ It represents evidence that male hormones are also implicated in the phenomenon of the testicular descent. The authors come to the following conclusions. Cryptorchid testes of the immature macaque have been observed to descend into the scrotum after adequate

administration of the male hormone, testosterone acetate and testosterone propionate. There is less edema and scrotal swelling than in the descent produced by gonadotropic substance. Processes considered largely responsible for the production of this descent, are (a) growth and elongation of cord elements, and (b) slight development of the scrotum to form more of a pouch for the retention of the testes. It is suggested that descent, produced by an anterior pituitary-like substance, may be in part due to stimulation of the secretion of male hormone substances.

Hormone treatment may be of value in (a) producing descent in certain cryptorchid cases, and (b) authorizing surgery at an early age instead of waiting until puberty to see if spontaneous descent might occur. Thus, some of the objectionable phenomena attendant upon cryptorchidism may possibly be avoided, and surgical treatment may be aided preoperatively by the development of cord structures and postoperatively by prevention of retraction and tension.

Treatment of sexual underdevelopment with synthetic male hormone substance is reported by J. B. Hamilton.⁸⁰ Synthetic male hormone substances were administered to a 27-year-old hypogonadal male who provided an excellent subject for evaluation of the effect of these materials. The hypogonadism and cryptorchidism, impotence, hot flushes, migraine, and mental attitude were treated with some degree of success. Brief discussion is given of the relation of these results in this clear-cut case to the subject of male hormone treatment with especial reference to cryptorchidism, hypogonadism, impotence, menopausal symptoms, migraine and acne. The probable influence of male hormones upon the pitch of the voice, the area of pig-

mented skin under the eye and the mental attitude is mentioned.

R. I. Dorfman, W. W. Greulich and C. I. Solomon⁸¹ examined the excretion of androgenic and estrogenic substances in the urine of children. The urines of 18 boys and 5 girls ranging in age from 6 to 16 years were assayed for androgenic and estrogenic activity. The androgenic activity varied from 1.1 to 32 I. U. per 24 hours, while the estrogenic activity ranged from less than 5 to 95 I. U. for the same period. Attention is called to the difference in the sex hormone excretion of children who, though of the same chronological age, differ from each other in the degree of their physical maturity.

R. B. Oesting and B. Webster⁸² employed colorimetric methods for the assay of sex hormones in the urine of children. They showed a gradual rise in androgen excretion from early childhood to adult life. There was a distinct rise in estrogen excretion at puberty. This was not true for androgen. It is suggested that estrogens play a more significant rôle in epiphyseal closure than androgens.

Gonadotropic Hormone—A review of the literature on the gonadotropic principle in the treatment of cryptorchidism is given by J. A. Bigler, L. M. Hardy and H. V. Scott.⁸³ These authors discuss the embryology and incidence of cryptorchidism as well as related animal experiments, their clinical applications and the surgical aspects of this anomaly.

From the observation of the result of treatment in 59 cases of cryptorchidism and from analysis of reports in the literature, N. Nixon⁸⁴ concludes that the undescended testis must be placed in normal position in the bottom of the scrotum before it has undergone the retrogressive changes which occur with puberty, if one is to prevent atrophy and

other complications. No result should ever be considered satisfactory unless the testes remain permanently in the bottom of the scrotum. Partial descent is not a satisfactory result and should not be reported as such. It would seem wiser to minimize the possibility of spontaneous descent, admitting that it does occur after puberty in some instances, and to endeavor to place the misplaced testis in the normal scrotum position either by injection of a gonadotropic substance or by orchidopexy before the patient has reached his ninth or tenth birthday. Should one choose to wait, some testes may descend spontaneously but irreparable damage will have been done to many.

Until recently the surgical treatment of cryptorchidism has been unsuccessful in too many instances. Surgical skill and uniformity of technic are essential to produce consistently the desired results. The *Torek operation* or one of its modifications, when properly carried out, will produce a satisfactory result in 80 per cent of the cases, a percentage far higher than that obtained in any other operation. The use of *endocrine therapy* is justifiable in the treatment of cryptorchidism. A course of injections of biologically standardized *extracts of pregnancy urine* given in adequate amounts over a limited period of time and in some cases repeated once or twice after several months of rest will cause complete descent in at least 25 per cent of the undescended testes. If after a reasonable period of time the optimum results have not been obtained, the child should be referred to a surgeon for repair of the anomaly. Because in some small boys the injections result in acceleration of penile growth and occasional appearance of secondary sexual characteristics, it seems advisable to postpone such treatment until the child is 7 or

8 years of age. Endocrine treatment at this age is advantageous. It not only brings about complete descent of at least 25 per cent of the testes; but when it fails to produce optimum results, it segregates the boys in whom the organs would not descend spontaneously after puberty which allows surgical repair of the anomaly before the retrogressive changes have occurred. In addition the treatment has the distinct advantage of making surgical repair easier by enlarging the testis and the cord structures in most instances and by increasing the size of the scrotum.

The differential diagnosis of pseudocryptorchidism and true cryptorchidism is discussed by J. B. Hamilton and G. Hubert.⁸⁵ There is described a technic of direct application of heat to the scrotum, inguinum and perineum for the purpose of obtaining relaxation of the muscles which produce spastic retention. This method plus the precautions, general procedures, and observations enumerated, permits differential diagnosis of intermittent and continuous retention of the testicle. Employment of this technic reveals the large percentage of pseudocryptorchid testes that are considered true cryptorchidism by usual tests, even by physicians experienced in the handling of children. The high incidence of pseudocryptorchidism masquerading as true cryptorchidism leads one to question the large percentages of spontaneous descent in supposedly true cryptorchidism. Further it may partially explain the discrepancy in the results of various authors in the treatment of cryptorchidism with endocrine preparations. It is suggested that some such precautions as outlined above be employed in future designation of true cryptorchidism since such procedures seem necessary to eliminate pseudocryptorchidism and since it would provide standardization of a

variable phenomenon so that the results of different groups of workers might be compared.

Precocious sexual development from an anterior pituitary-like principle is reported by W. O. Thompson and N. J. Heckel.⁸⁶ Changes simulating premature puberty have been produced in 3 boys, 4, 7 and 9 years of age, by the administration of the *anterior pituitary-like principle* from the urine of pregnant women. These changes consisted of an increase in the size of the penis, scrotum and prostate, increased masculinity, a growth of pubic hair and a change in the pitch of the voice. In contrast to the marked growth of other parts of the genitalia, the testes showed very little change in size. All the boys were of normal body contour and had a normal sized penis before treatment was started. The 4-year-old boy had an atrophic left testis which did not increase in size with treatment. The other 2 boys had undescended testes, and in 1 of them an unsatisfactory attempt at surgical correction had been made. In both patients the testes descended to the normal position with treatment. Some genital growth had been produced with the same material in 16 of 33 patients with undescended testes and in 14 patients, including 2 of the 3 boys who developed changes simulating premature puberty, it was marked. However, descent was produced in only 23 per cent of the total number of undescended testes, showing that genital growth may occur without descent of the testes. The treatment for undescended testes with an anterior pituitary-like principle should be stopped before genital growth becomes marked. If this rule is followed, it would appear that in the present state of our knowledge, its routine use is justifiable and desirable.

Hypoglycemia

A. F. Hartmann and J. C. Jaudon⁸⁷ analyzed 286 cases of hypoglycemia occurring in children. Their classification includes 3 groups: (a) Normal newborn infants; (b) infants born of diabetic mothers, and (c) children developing recurring attacks of very severe hypoglycemia who seem to be insulin hypersensitive or intolerant chiefly because of the lack of proper opposing secretions (adrenal and pituitary). The authors come to the following conclusions: Hypoglycemia during the first 4 or 5 days of life occurs quite regularly in normal newborn infants and seems to be due to an imperfectly developed regulatory mechanism which creates a state of relative hyperinsulinism.

A similar period of hypoglycemia with the development occasionally of such very severe manifestations as convulsions and collapse occurs in infants born of diabetic mothers. The greater fall in blood sugar in such infants (sometimes with a striking absence of symptoms) seems more often referable to an increased physiologic hyperactivity of the islands of Langerhans than to the development of islet cell hypertrophy or hyperplasia and may be prevented or controlled quite effectually by the combined use of epinephrine and dextrose injection as emergency measures, and the prophylactic starting of complemental milk and carbohydrate feedings immediately after birth. The most careful observation of such infants for the first 4 or 5 days of life seems almost necessary. The natural tendency to the development of hypoglycemia in the first few days of life may be greatly intensified also by adrenal and intracranial hemorrhage. The demonstration of intolerance or increased sensitivity to insulin in subjects who have recurring attacks of

severe hypoglycemic symptoms seems of considerable diagnostic value during symptom-free intervals. There is some reason to believe that in such cases the susceptibility to hypoglycemia is familial.

The close relationship between the diencephalon and the endocrine glands is disclosed by certain syndromes, which are apparently due to an endocrine disturbance, although the syndrome cannot be explained by the impairment of any single gland. F. Albright, W. B. Scoville and H. W. Sulkowitch⁸⁸ describe 2 cases of a syndrome in males, characterized by osteitis fibrosa disseminata and areas of cutaneous pigmentation. In the case of 1 male, the bone age was precocious, suggesting that even in the male sex some precocity may occur. It is known that the syndrome mentioned occurs with sexual precocity in females. In 1 case on the same side as the cutaneous lesions and the majority of the bony lesions, abdominal and cremasteric reflexes were absent and there was decreased sensitivity to pain. These findings strengthen the hypothesis that the whole syndrome is due to a disseminated neurological lesion. Evidence from the literature is cited showing that sexual precocity may be due to lesions of the walls of the third ventricle and of the hypothalamus. Attention is called to the fact that 2 patients with the syndrome had hyperthyroidism as well. Metabolic studies on 1 patient showed that more than the normal amount of calcium was excreted in the urine.

A case of osteodystrophia fibrosa combined with precocious puberty, pathologic pigmentation of the skin and hyperthyroidism is reported by D. J. McCune and H. Bruch.⁸⁹ This syndrome has been observed in a girl from her second year of life on to the tenth year. Symptoms of hyperthyroidism started at the age of 4 years. The plasma phosphatase activity was increased. In other

respects numerous chemical examinations of the blood gave normal results.

Balance studies of the calcium and phosphorus metabolism have yielded findings quantitatively similar to those obtained for healthy children. The patient did not show hypercalciuria. Biopsy of the bone has not provided clear-cut information concerning the precise hypercalciuria classification or the etiology of the osseous dystrophy. The evidence derived from measuring the concentration of parathyroid hormone in the blood and of gonadotropic and estrogenic substances in the urine is negative. A very good review of the literature of similar cases concerning 8 or possibly 9 females with an identical condition was made. Reports of 5 males showing fibrocystic osteodystrophy and pathologic pigmentation of the skin without precocious puberty are also mentioned. Critical scrutiny of the available evidence relating to the collected cases does not provide adequate grounds on which to base a satisfactory conjecture concerning the nature of this factor. An atypical variety of von Recklinghausen's neurofibromatosis, an unusual type of xanthomatosis or an unidentified disease of the hypothalamic region, could be considered the fundamental pathologic condition.

J. Warkany and A. G. Mitchell⁹⁰ have discussed the relation of endocrine disturbances to certain heredogenerative symptoms. They point out that great care should be exercised in determining whether all defects and symptoms found in a patient with an endocrine disturbance are necessarily causally related to it. Some of them certainly are not but represent rather associated hereditary or developmental defects. It is therefore not surprising that a hormone administered to different patients with endocrine disturbances should give widely different results or have no effect at all

on certain associated symptoms. Until recently, only a few physiologically or pharmacologically active preparations of endocrine glands, such as thyroid extract, epinephrine or pitressin, were available. Most of the other so-called endocrine preparations were either inert or largely so. Now there is an increasing number of products which affect the body. As yet, little is known of their quantitative effects, their unwanted by-effect, and too little, also, of their purity. This confusion must not be increased by the attempt to treat with endocrine products conditions which are not caused by endocrine disturbance.

Obesity

The creatinine coefficient is recommended as a measurement of obesity by N. B. Talbot.⁹¹ Obesity is defined as an accumulation in the body of an amount of subcutaneous fat which is excessive in relation to the amount of muscle. Persons of normal weight who show such a disproportion should be considered obese and a person who is overweight but has a superior development of the muscular system should not be considered obese. The proportion of muscle in the body may be derived from the ratio of the amount of creatinine excreted in the urine to body weight. This ratio—mg. of creatinine per 24 hours/kg. of body weight—was named "creatinine coefficient" by Shaffer, who found that the creatinine coefficient of normal men varies from 14.5 to 31.4. According to Talbot the average creatinine coefficient of obese, normal and lean children were found to be 14, 20.4 and 30.7, respectively. The weight of the muscles as calculated from the output of creatinine of these groups constitutes, respectively, 25, 37 and 55 per cent of the body weight. The author concludes that the creatinine coefficient combined with clinical appraisal

is an accurate index of obesity. Physiologic and pathologic problems concerned with the relative amount of muscle in the body may be studied by the determination of the excretion of creatinine

Parathyroid Glands

F. Albright, E. Bloomberg, T. Drake and H. W. Sulkowitch⁹² have made a comparison of the effects of A. T. 10 (dihydrotachysterol) and vitamin D on calcium and phosphorous metabolism in hypoparathyroidism. Since the paper by F. Holtz⁹³ in 1933 there have appeared a considerable number of articles on a photochemical derivative of ergosterin designated dihydrotachysterol or A. T. 10. From these articles one gets the impression that A. T. 10 and vitamin D affect calcium metabolism in much the same way with the 1 difference that A. T. 10 is not antirachitic. This combination of facts appears surprising, since at first thought it is hard to believe that any substance chemically so closely related to vitamin D could have so similar an action on calcium metabolism and still not cure rickets. It thus becomes of interest to know the exact manner in which this new substance affects calcium and phosphorus metabolism and wherein its action differs from that of vitamin D. The results of the study showed that the action of A. T. 10 and of vitamin D on the calcium and phosphorus metabolism of 3 patients with hypothyroidism was fundamentally the same, that is, to increase calcium absorption from the gut and to increase phosphorus excretion in the urine. The ratio of the latter action to the former, however, was apparently greater with A. T. 10, which may explain why A. T. 10 is not antirachitic. The action of vitamin D was slower and lasted longer than that of A. T. 10. The parathyroid hormone resembled A. T. 10 in regard to its

property of causing a markedly increased urinary excretion of phosphorus, but differed in that it probably had no primary action on calcium absorption from the gut. Because of the similarity between the actions of the parathyroid hormone and of A. T. 10, the latter drug is a most efficacious therapeutic agent in the treatment of hypoparathyroidism.

A. E. Hansen, I. McQuarrie and M. R. Ziegler⁹⁴ have made a study of the effect of parathyroid extract on the plasma phosphatase and on the serum proteins, calcium and inorganic phosphorus in 4 cases of osteogenesis imperfecta. Three extended experiments on the effect of large doses of irradiated ergosterol on these same blood constituents were carried out in 2 of the 4 cases. The plasma phosphatase activity of these patients was found to be within normal limits under ordinary conditions but was greatly depressed by both parathyroid extract and viosterol. The serum calcium, on the other hand, was definitely increased by both agents in all cases. The inorganic phosphorus of the serum was decreased by the administration of parathyroid extracts in 3 cases and increased slightly in 1. The level of serum inorganic phosphorus was not significantly altered by the irradiated ergosterol except in the case of the youngest patient. In this instance it was merely increased from a subnormal to a normal level. The serum proteins were essentially unchanged by either parathyroid extract or viosterol.

In the main, the effect of the parathyroid extract and of large doses of viosterol were alike in producing negative balances of phosphorus, and calcium in these cases as they do in normal subjects. Such agents are, therefore, contraindicated in osteogenesis imperfecta because they tend to accentuate the functional disturbance already present. Thera-

peutic procedures which would increase the phosphatase activity might, on the other hand, have a beneficial effect in this disorder.

Pituitary

Growth Hormone—N M Taylor⁹⁵ discusses the treatment of pituitary dwarfism with growth hormone and presents 8 cases of endocrine growth deficiency, 7 males and 1 female. The ages ranged from 11 to nearly 16 years at the onset of treatment. Anterior pituitary growth hormone and thyroid extract were employed concomitantly as therapeutic measures to accelerate growth. Treatment in 3 cases was continuous for 2 years or more, in 4 cases over 1 year and in 1 case for 8 months. Two cubic centimeters of *antuitrin G* 3 times weekly gave apparently favorable developmental response in 7 cases. In 1 case increasing the dosage of growth hormone did not further accelerate the previous increase in height. No phenomena were noted in this small series which would postulate the existence of a period refractory to treatment or an anti-hormone substance. Seven of the children presented serious behavior problems and 5 of these have adjusted satisfactorily. One child who failed to adjust in behavior, displayed no accelerated growth under growth hormone therapy.

Prolactin J R Ross⁹⁶ describes the effect of prolactin on the secretion of woman's milk. Prolactin was administered intramuscularly to mothers whose daily breast milk excretion on the fifth and sixth days was less than 400 cc. The injections were given twice daily over a 2-day period. One group of patients received a total of 400 units, whereas the second group received a total of 1000 units. A control group of patients received intramuscular injections of normal saline. The higher concen-

tration of prolactin administered appeared to increase slightly the secretion of breast milk during the remainder of the stay in the hospital. Of much more significance, however, seemed the fact that 7 out of 11 patients receiving this higher concentration of prolactin, whose records could be followed after discharge from the hospital, nursed their infants completely, whereas out of 8 such observed patients receiving the lower concentration of prolactin, only 2 were able to nurse their infants completely.

Of the 8 controls observed who received normal saline, only 1 nursed her infant completely. Rather severe local reactions followed the injection of the larger amount of prolactin. It is probable that further purification of prolactin will eliminate these reactions. The administration of prolactin apparently has no effect on the fat, protein or ash content of the breast milk secreted. The galactagogue effect obtained justifies the further investigation of the value of this product. The urinary excretion of estrin in these cases was within the range found during the normal menstrual cycle.

Thymus

D J Ingle⁹⁷ investigated the effect on the thymus of administering massive amounts of cortin to normal rats and to rats which had been hypophysectomized. He comes to the conclusion that the administration of large amounts of cortin given in the drinking water causes marked involution of the thymus in the intact rats. A loss of weight occurs in these animals which cannot be satisfactorily accounted for by the small reduction in the intake of food. In the hypophysectomized rats in which the adrenal cortices have been maintained at normal size with adrenotropic hormone, additional treatment with cortin hastens atrophy of the thymus.

H. M. Evans, H. D. Moon, M. E. Simpson and W. R. Lyons⁹⁸ found that complete regression of the thymus occurred after administration of adrenocorticotrophic hormone. With reference to the foregoing paper the authors come to the conclusion that the atrophy of the thymus is due in part to the increased production of cortin after administration of adrenocorticotrophic hormone, but it does not eliminate the possibility that increased production of male or female sex hormones in the adrenal cortex may be a contributing factor.

A study of the biological effects of thymectomy supplements a previous paper by N. H. Emhorn and L. G. Rowntree⁹⁹ on the same subject. Thymectomy in successive generations of parent rats caused a retardation in growth and development in the offspring. This retardation is amplified if thymectomy is carried through succeeding generations to the sixth. Thymectomy in successive generations of males mated to normal female litter mates did not affect the growth and development of the offspring, nor did thymectomy in successive generations of females mated to normal male litter mates. Both parents must be thymectomized in order to produce retardation in the rate of growth and development of the offspring. The results obtained in these studies seem to indicate that the thymus glands of the parents are concerned in growth and development of the offspring.

Thyroid

L. Wilkins¹⁰⁰ describes a method of following and comparing the rates of growth, osseous development and mental development of cretins as a guide to thyroid treatment. The administration of adequate doses of thyroid always causes a marked acceleration in the developmental rates. The bone development

always progresses rapidly toward the normal level. The growth increases less rapidly, but usually parallels or exceeds the normal rate, whereas the mental development in some instances continues to lag behind the normal rate. The developmental rates, especially the rate of osseous development, serve as a reliable guide to the adequacy of thyroid treatment over long periods, whereas the clinical condition of the patient and the measurements of the basal metabolic rate or blood cholesterol may give a deceptive picture of the amount of improvement. It is probably necessary to produce a mild degree of hyperthyroidism in order to accelerate the developmental rates sufficiently to allow the retarded hypothyroid patient to regain his lost years and approach his normal age level. One should not hesitate to give sufficient thyroid, provided that unpleasant toxic symptoms do not occur.

B. Benjamin and P. R. Miller¹⁰¹ describe a disturbance of ossification involving the capital epiphysis of the femur in children suffering from deficient function of the thyroid gland. Maldevelopment may be of 2 varieties. One of these affects the structure of the epiphyseal plate in such a manner as to give rise occasionally to slipping of the epiphysis. The other is in the nature of osteochondrosis of the head of the femur. In either case deformities ensue which lead to the appearance of coxa vara. On the basis of the osseous changes found in cretinism, an explanation is offered to account for the slipping of the epiphysis. What may be designated as a mesh type of union, characterizes the junction of the epiphysis and diaphysis in normal growing bones.

A powerful interlocking of cartilage and bone is achieved by the interdigitation of the gear teeth of the calcified

lattice with the opposing filamentous processes of bone forming marrow. In cretins, however, the remarkably intimate association occurring at the normal epiphyseal plate is replaced by a disc type of configuration in which a flat zone of solidly calcified cartilage is in apposition with a transverse layer of bone. It is pointed out that the disc type of union may be incapable of resisting stresses which are well borne by the normal mesh type. As a result, the epiphysis in children with hypothyroidism may be dislodged. The possibility is mentioned that the disc type of epiphyseal plate may be a factor in the etiology of slipped epiphysis in children without hypothyroidism who have been exposed to trauma during certain periods of their development.

The second type of lesion, osteochondrosis of the head of the femur, arises from an irregular bony development of the epiphysis with the persistence of numerous islands of uncalcified cartilage. The roentgenographic features are discussed in relation to the pathologic changes which take place. The osteo-

chondrosis is insidious in character and in the cases described here was discovered by means of roentgenograms. Subsequent examinations have led to the conclusion that it may be possible to detect the condition clinically. The finding in children with hypothyroidism of limitation of motion at the hip chiefly in internal rotation constitutes presumptive evidence of the presence of the disease of the hip.

Cretinoid epiphyseal dysgenesis is presented by W. A. Reilly and F. S. Smyth.¹⁰² In some children having severe hypothyroidism resembling that of the true cretins, many of the epiphyses develop abnormally and have the following characteristics. There are multiple loci of calcification, the calcification is slow, abnormal epiphyses occur in many parts of the skeleton, the distribution usually is bilateral, the process occurs generally in the capital epiphysis, there may never be normal structure without treatment. When thyroid extract is used, normal epiphyses developed in as short a time as 6 to 12 months.

GENITOURINARY SYSTEM

By WALDO E. NELSON, M.D.

Abnormalities of Urinary Tract

In a discussion of nonobstructive dilatations of the upper urinary tract in children, A. B. Hepler¹⁰³ states that 2 types of functional imbalance at the ureterovesical junction are recognized: (*a*) Increased tonicity, or spasm, and (*b*) absence of the usual active relaxation synchronous with the termination of ureteral peristalsis, or achalasia.

It is stated that the resistance to ureteral emptying caused by these dysfunctions sets in motion the same physical and dynamic factors which produce

dilatation in mechanical obstructions. Compensation is more apt to occur in functional imbalance than in mechanical obstruction, since resistance to ureteral emptying is apt to be less unyielding, hence the observation of ureterectasis out of proportion to the pelvic dilatation and in the absence of elongation and tortuosity. It is suggested that in some instances congenital idiopathic dilatation considered as a primary embryologic developmental defect may in fact be secondary to a segmental imbalance or abnormal activity of the sphincter.

In 1 child the author observed the association of megacolon and megaloureter and suggests that the mechanism of their pathogenesis may be similar.

While the author states that the indications for treatment of a condition so little understood are not clearly defined, he suggests that attention may well be directed to the possibility of correction through surgical treatment of the sympathetic nerve supply. This is based on the supposition that the functional imbalance may be dependent upon abnormalities of the nerve supply for the autonomic system. With persistent infection and ureteral dilatation, the use of an indwelling ureteral catheter, pelvic lavage and other accepted methods are indicated. With decompensation and secondary obstruction and infection, the indications for nephroureterectomy are the same as with the obstructive lesions.

An instance of urinary retention, overflow incontinence, and severe constipation due to malformation of the sacral portion of the spinal cord in a boy 14 years of age is reported by P. C. Bucy, C. Huggins and D. N. Buchanan.¹⁰⁴ Section of the presacral nerve greatly improved the function of both the bowel and the bladder, and this improvement was maintained for more than 3 years after the operation. This improvement, the authors believe, was due largely to relaxation of the sphincter innervated by the sympathetic nervous system. This is in contrast to the opinion of Learmonth who attributes the beneficial effect of section of the presacral nerve in such cases to the removal of the "brake" action of the sympathetic nerve on the detrusor muscle, i. e., the inhibition of contraction of the detrusor muscle. The authors doubt that this effect is of great significance, if it is present at all. Their opinion regarding the effect of the sympathetic nerve fibers was based upon

observations made during operation by stimulation of the peripheral end of the cut presacral nerve. This stimulation resulted in: (a) Contraction of some "sphincteric" structure, probably smooth muscle of the prostatic urethra and the prostate at the junction of the prostatic and membranous portions of the urethra, which they have termed the "sympathetic external sphincter"; (b) diminution in the size of the verumontanum, possibly as a result of vasoconstriction, and (c) emission of prostatic and seminal fluid.

Enuresis

Nocturnal enuresis or bed-wetting without diurnal incontinence is generally considered to be due to psychologic factors or lack of training. H. Bakwin,¹⁰⁵ however, believes that in the large majority of children with true enuresis, the basis is organic and resides in an anomalous innervation of the bladder (irritable bladder) and that faulty training and psychologic factors are important contributory factors. The "irritable bladder" is apparent in infancy and persists throughout life. It manifests itself by frequency and urgency, particularly in response to nervous tension or cold.

Treatment—Since children with irritable bladders are difficult to train, psychologic conflicts associated with the training situation are more likely to arise than in normal children. In older children endowed with this abnormality in urination, psychologic maladjustment frequently expresses itself as enuresis. The author recommends *belladonna* in the treatment of irritable bladder. This should be combined with training, suggestion and adjustment of the psychologic environment. Belladonna, to be effective, must be given in large doses. The recommended starting dose is 5 drops of the tincture of belladonna (equivalent to $\frac{1}{600}$ grain of atropine) 3

times a day for a 5-year-old child. The dose is increased 3 drops each day (1 drop each dose) until distinct improvement in the urinary symptoms or flushing of the skin appears. As much as 20 or 30 drops 3 times a day is often tolerated. It is stated that no improvement is to be expected until the individual dosage reaches about 15 drops. It is recommended that the dosage be increased to 20 drops if the child will tolerate it, even though symptoms disappear with a smaller amount. Belladonna should be continued for 3 to 4 weeks or longer after the enuresis has ceased in order to permit the habit of voluntary control to become established. The author believes that enuresis, solely on a psychogenic basis, is rare and is to be distinguished from factitious enuresis, *i e*, intentional wetting. Belladonna is useless in this condition.

A limited degree of success is reported by M. Molitch and S. Poliakoff¹⁰⁶ in the treatment of enuresis with **benzedrine sulfate**. Eight of 22 children with chronic enuresis ceased wetting the bed when a placebo was administered. Of the 14 children who failed to respond to the placebo, 12, or 86 per cent, were entirely relieved of their enuresis when given benzedrine in increasing doses terminating at 5 to 25 mg daily. All 22 of the children reverted to bed wetting within 2 weeks after the discontinuance of both the placebo and benzedrine. It is suggested that the placebo or benzedrine may contribute toward better habit formation, especially when no organic cause is present. However, because of untoward results which have been reported with benzedrine, extreme caution in its use should be practised.

Foreign Bodies

The clinical findings resulting from foreign bodies in the vagina or bladder

of children are described by P. Rosenblum and A. E. Jones.¹⁰⁷ Roentgenograms of 5 of them are shown in Figs. 1, 2, 3, 4 and 5. The authors caution that frequent, painful urination with blood and pus in the urine should always make one suspicious of a foreign body. The examination should include roentgenograms or cystoscopy or both.

Infection of the Lower Urinary Tract

Definite evidence that infection of the renal parenchyma may occur from the pelvis of the kidney has been presented by H. F. Helmholtz.¹⁰⁸ This author previously demonstrated that 1 of the avenues of infection of the renal pelvis was by the ascending route. The present observations indicate that, characteristically, even with intense pyelitis produced by direct injection of bacteria into the pelvis of the kidney a barrier exists to the spread of the infection into the renal parenchyma. Stasis in the urinary passages appears to be the determining factor in the breaking through of an infection from the pelvis of the kidney to the parenchyma. There are at least 4 ways in which infection may enter the renal parenchyma: (*a*) By ascent of the collecting tubules producing local lesions in the papilla, medulla or cortex, (*b*) by extension along the perivascular lymph spaces of the large vessels entering the substance of the kidneys, (*c*) by the vascular route, either arterial or venous, by direct infection from the adjacent infected pelvis, and (*d*) by direct extension through the wall of the pelvis into the renal parenchyma at any point where the parenchyma lies in direct contact with the pelvis.

The important point brought out by this work is that when the lower urinary tract is unobstructed, pyelitis may exist without parenchymal involvement. The

kidney has a protective mechanism by which the infection is kept out of the kidney proper and this barrier seemingly remains intact as long as there is no obstruction to the outflow of urine. It is broken down in less than 24 hours when

there is obstruction. The clinical implication is evident. It is of the utmost importance to maintain adequate drainage in all cases of infection of the lower urinary tract and in the acute stages of urinary infection, the most important



Fig 8 Case 1 Tailor's pin in bladder Embedded in stone
 Fig 9 Case 2 Hairpin in bladder
 Fig 10 Case 3 Foreign body in vagina
 Fig 11. Case 4 Marble in vagina
 Fig 12 Case 6 Hairpin in bladder embedded in a soft stone which did not show in the skigram (J Pediat. June, 1938)

object of treatment is adequate production of urine to wash out the thick, purulent exudate and so prevent stasis.

The late effects of acute pyelitis in girls have been studied by L. R. Wharton, L. A. Gray and H. G. Guild¹⁰⁹. Thirty girls and young women who had been hospitalized some years before for

health at the time of the examination. Only 1 had been treated for any urologic disease since her childhood pyelitis. The remaining 28 had average good health and most were in excellent health. The vast majority had no complaints whatever. Symptoms, when present, could be elicited only by questioning. In view



Fig 13—At the age of 4 years this patient had an attack of acute urinary infection, she had no further urinary disorders. Follow-up study at the age of 20 showed occasional leukocytes in the urine and colon bacillus infection. The upper part of the ureters are dilated and redundant, the right ureter is redundant and the left ureter is angulated. The patient is in excellent general health, the only symptom being occasional pain in the back. (Courtesy, J. A. M. A., Nov. 13, 1937)

1 or more attacks of acute urinary infection were recalled for clinical examination. The examination carried out was as follows: (a) History, (b) physical examination, (c) examination of catheterized specimen of urine from the bladder; (d) culture of urine from the bladder; (e) intravenous phenolsulfon-thalein test for 30 minutes, and (f) intravenous urography. Only 2 of the 30 girls and young women were in poor

of the apparent good health of these young women, the results of this check-up examination are extremely interesting. The authors found that 17, or 57 per cent, had definite abnormalities in the urinary tract at an average time of 9.6 years after their last attack of pyelitis. Of 9 who had had only 1 attack of urinary infection in childhood, 6 now have urinary abnormalities. Of 21 who had recurring infections during childhood, 11

now have urinary abnormalities. At the time of the re-examination, 10 had mechanical abnormalities, as shown by intravenous urography, 10 had varying numbers of leucocytes in the catheterized urine, and in 15 instances cultures of the urine were positive. Two of them had small stones. One girl of 15 years of age

be made. If a residual lesion is present, it should receive appropriate treatment. Helmholtz in discussing this paper points out that it was not stated in how many instances the infection persisted. He states that a patient should not be discharged until one knows that the infection is actually cured. By cured is not



Fig. 14—At the age of 4 years this patient had an attack of pyelitis due to the colon bacillus. Her present age is 21 and her general health is good. She is married and has 1 child, born in 1934. The pregnancy was complicated by toxemia. The patient now has beta streptococci in the urine. The urogram shows slight hydronephrosis, with redundancy of the upper part of the right ureter. (Courtesy, J. A. M. A., Nov. 13, 1937.)

had a functionless kidney with practically no symptoms. Three of the young women had borne children; 1 had pyelitis while pregnant.

One cannot but agree with the authors when they conclude that on the basis of this study urinary infections of girls cannot be dismissed casually. They advise that after symptomatic recovery is complete and after the child has been well for several months, a check-up examination such as employed in this study should

mean the absence of pus in the urine but the absence of bacteria determined by culture after discontinuation of the treatment. Only in this way is it possible to prevent a continuation of infection as illustrated by this series. Helmholtz feels certain that those children who had normal urinary tracts could have had their infections cleared up with intensive therapy even in the days when methenamine was employed, and certainly at the present time with the new drugs which are

available. When infections do not clear up rapidly, a urologic examination is essential.

In vitro experiments by H. F. Helmholz¹¹⁰ have shown that **prontylin (sulfanilamide)** has marked bactericidal action on all of the common bacteria found in infections of the urinary tract with the exception of streptococcus fecalis. Sulfanilamide produces a urine that is strongly bactericidal. The dosage which is necessary to produce bactericidal urine is considerably less than doses which have been given, without any ill effect, for infections with streptococci. The ease of administration of sulfanilamide during the acute stage of the disease, its bactericidal action in both acid and alkaline urine, although apparently more effective in alkaline urine, and its successful use in cases of renal insufficiency, make it a drug of great usefulness in the treatment of acute and chronic infections of urinary tract. Although the exact dosage has not been established, the following are the dosages currently recommended by the author: For infants, 0.33 to 0.5 Gm. per day; for children 2 to 3 years of age, 0.5 to 1.0 Gm. per day; for children 4 to 6 years of age, 1.0 to 1.5 Gm. per day; for those 5 to 11 years of age, 1.25 to 1.75 Gm. per day; and for those 12 to 15 years of age, 1.5 to 2.0 Gm. per day. After 4 or 5 days of these dosages, the amounts can be reduced to three-fourths or two-thirds of the original dose. Mandelic acid is still the drug of choice for infections with the streptococcus fecalis.

Clinical data are presented by A. M. Butler¹¹¹ demonstrating that hypertension not infrequently is associated with pyelonephritis before there is any appreciable diminution in renal function and that hypertension which is secondary to unilateral pyelonephritis may disappear when the involved kidney is removed. In

the majority of the cases there was no definite proof that the pyelonephritis preceded the hypertension. In 1 instance, however, a patient who was found to have a unilateral pyelonephritis developed during the course of the next 8 months hypertension and cardiac failure. The removal of the 1 infected kidney was followed by clearing of the urine and the return of the blood pressure to normal where it had remained for 20 months. In this case there was strong evidence that the pyelonephritis preceded the hypertension and in some way had a causal relation to it. The question is raised but not answered why some patients with pyelonephritis develop hypertension before renal insufficiency, while some develop it only after the renal damage has become marked and still others die in uremia with very little hypertension.

Kidney Function Test

Additional data on the Addis sediment count have been compiled by A. W. Snoke¹¹² in 202 supposedly normal children. Snoke's figures for the number of casts and red blood cells excreted in 12 hours were in close agreement with those reported by Addis and Lyttle. However, Snoke found a higher excretion of protein for the 12-hour period and suggests that the upper limit of normal protein should be raised to 55 mg. The comparison of the standards for the Addis sediment count are shown in Table —. One case of previously unsuspected and unrecognized latent glomerular nephritis was discovered by the Addis technique among 202 presumably normal children.

Malignancies

In a well-written article on primary malignant tumors of the urogenital tract of infants and children, M. F. Campbell¹¹³ states that radiation therapy merits first place in their immediate

TABLE I
COMPARISON OF STANDARDS

	Addis			Lyttle			Snoke			Proposed Upper Limits
	Average	Lowest	Highest	Average	Lowest	Highest	Average	Lowest	Highest	
Casts	1,040	0	4,270	1,085	0	12,916	1,230	0	29,000	10,000
Red blood cells	65,750	0	425,000	15,181	0	129,000	81,600	0	800,000	600,000
White and epithelial cells	322,500	32,400	1,835,000	322,184	9,000	2,822,000	/	/	/	2,000,000
Protein				18.5	3	47	28.5	5	90	55 mg

(J. Pediat., April, 1938)

treatment. Only by adequate radiation, both preoperatively and postoperatively by the divided daily dose method, together with judicious surgical intervention, can one hope to reduce the high mortality rate. Since the article does not lend itself to abstracting, the reader is referred to the original for details of symptoms, diagnosis and treatment of the various tumors described.

Nephritis

Acute Hemorrhagic Nephritis—

The importance of cardiac complications in acute hemorrhagic nephritis is pointed out by M. I. Rubin and M. Rapoport.¹¹⁴ In a series of 55 children with acute hemorrhagic nephritis, the authors observed 14 children with varying degrees of cardiac involvement during the acute stage of their illness. Two deaths were attributed to acute heart failure.

The clinical evidences of cardiac involvement and failure observed in the authors' cases of acute hemorrhagic nephritis were

1. Dyspnea, tachypnea and cough
2. Cardiac enlargement, demonstrable both by physical examination and in teleoroentgenograms
3. Muffled heart tones
4. Rapid heart rate
5. Murmurs, usually a mitral systolic murmur. This murmur was often the last evidence of cardiac damage to disappear

6. Gallop rhythm. This was present in the patients with more advanced heart failure.

7. Enlargement and tenderness of the liver.

8. Engorgement of the venous system.

9. Pulmonary edema.

10. Peripheral edema. It was impossible to estimate how much of the edema in a given case was due to damage of the kidney itself and to what extent the heart failure was contributing. However, after digitalization of the nephritic patients with heart failure there was often a striking decrease in the amount of edema.

11. Electrocardiographic changes indicative of varying degrees of myocardial damage.

It is suggested that during the acute phase of the disease there are 2 factors which may affect the heart adversely, *viz.*, myocardial damage and increased peripheral vascular resistance (hypertension). In regard to myocardial damage, it is suggested that it may be possible that the same infective agent responsible for the acute nephritis damages the heart. The second factor, hypertension (which is evidence of increased peripheral resistance brought about by vasospasm), is the agent immediately responsible for the impairment of cardiac function. In this series, hypertension was present in all patients exhibiting signs of cardiac insufficiency. The usual response of the heart to an increase in peripheral resistance is dilatation of the left ventricle, with ultimate hypertrophy. In those instances in which

the heart is primarily involved by the disease it is likely to fail under the added load of a sudden increase in peripheral resistance. The occurrence of heart failure is thus dependent on 2 factors—the extent of the myocardial damage and the degree of hypertension. The authors emphasize that in the hypertensive child elevation of the diastolic pressure is of greater import and is a more constant

in a case of acute nephritis which makes it obvious that heart failure is not an isolated phenomenon but is intimately related to other factors. This is illustrated graphically in Fig 00.

In those cases where the heart appears normal and when there is no marked elevation of the blood pressure and when the major disturbance is the retention of metabolites caused by decreased ac-

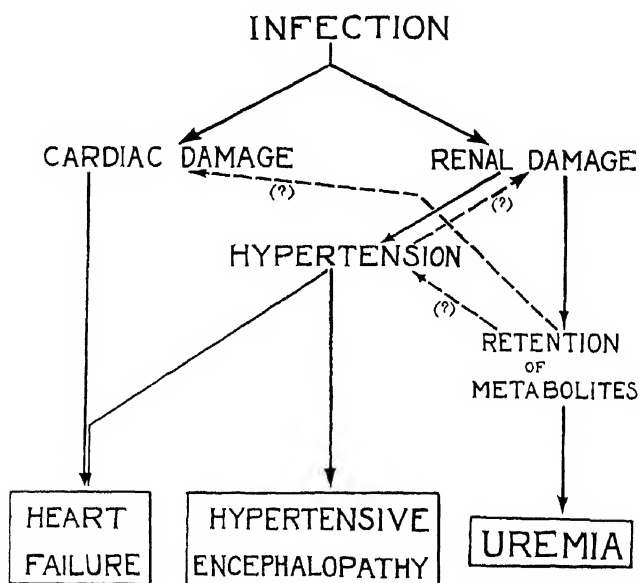


Fig 15—Diagram showing interrelations of the various factors operative in a case of acute nephritis. (Am J Dis Child, Feb, 1938.)

finding than elevation of the systolic blood pressure.

If the child survives the acute stage, the *prognosis* is apparently good. In only 1 of the patients in this series who had cardiac involvement was there any evidence of permanent cardiac damage, and this patient now has evidence of chronic hemorrhagic nephritis.

Treatment—The authors have been unable to dissociate the treatment of the cardiac manifestations of acute hemorrhagic nephritis from the general management of the disease itself. This is based on a consideration of the interrelations of the various factors operative

of the kidney, therapy may include the *forcing of fluids* in an attempt to dilute the toxins and produce diuresis. When severe acidosis is present, the administration of *alkalis* should be considered. Repeated readings of the blood pressure should be taken. If the blood pressure should rise or if there should occur any symptom or sign referable to myocardial damage, *fluids should be restricted* and other treatment instituted as indicated.

In cases of acute hemorrhagic nephritis in which hypertension is present, the control of the hypertension is important with reference to the encephalo-

pathic syndrome, but it is of even more moment in the prevention of cardiac failure. **Magnesium sulfate** is administered to relieve vasospasm. The recommended dose is 0.2 cc. of a 50 per cent solution per kg. of body weight. The effects of a single dose are usually prompt. The systolic and diastolic pressures begin to subside within an hour and remain down for several hours. The full dose may be repeated at 4-hour intervals. A single, calculated dose of magnesium sulfate may have no effect. In such instances the authors feel that it is safe to repeat the injection at shorter intervals. It is pointed out that when there is marked renal impairment with low urinary output and with marked retention of metabolites, it is possible that the accumulation of magnesium in the body may exert a narcotic effect. In such instances the **soluble calcium salts** may be employed as an effective antidote.

The authors believe that fluids should be restricted in cases of acute hemorrhagic nephritis with hypertension, since by the administration of liberal amounts of fluid there is danger of producing a further elevation of blood pressure and precipitating a cardiac catastrophe. During the period of acute hypertension, the fluid intake is arbitrarily limited to from 750 to 1000 cc daily. Since the hypertension is usually of short duration, fluids are restricted only until the blood pressure has subsided to a level within relatively normal limits, after which fluids may be given in liberal amounts to further diuresis.

When there is evidence of cardiac damage, supportive measures for the heart are instituted in addition to the use of magnesium sulfate and the limitation of fluid intake. **Digitalis** is administered by the rapid method to children with signs of cardiac failure; the dose is 45 mg. of powdered leaves per kg.

of body weight (usually given hypodermically as fat-free tincture in a period of 12 hours). After administration of the complete digitalizing dose it is usually found unnecessary to continue with a maintenance dose. When the cardiac involvement is severe, **morphine** is found to be valuable. The administration of **oxygen** appears to benefit patients with respiratory symptoms resulting from heart failure. **Phlebotomy** was employed on 2 occasions when there was more advanced cardiac failure. Fifty per cent solution of dextrose was administered to several patients but the authors were unable to evaluate its effect.

Nephrosis

Metabolic studies on 5 nephrotic children have been carried out during periods lasting from 42 to 255 days by A. G. Mitchell, C. R. Rittershofer, C. C. Wang, M. Kaucher, M. Wing and C. Hogden.¹¹⁵ The effects of diuretics and dietary treatment varied greatly in producing temporary changes. However, no prolonged general improvement, including disappearance of edema, was accomplished with any procedure. The values for basal metabolism of all patients were within normal limits according to the standard of Benedict and Talbot, and, with 1 exception, to the standard of Harris and Benedict. From the determinations of caloric intake and caloric loss, calculations were made for the percentage absorption of energy and the expenditure of energy for growth, digestion and activity. These values agreed with data obtained for normal children. This indicates that the energy exchange of a nephrotic patient is normal.

That there may be some relation of the carrier state to pneumococcal peritonitis in young children with the nephrotic syndrome is suggested by C. M.

MacLeod and L. E. Farr.¹¹⁶ In 6 children with the nephrotic syndrome who developed pneumococcal peritonitis, the type of pneumococcus recovered from the nasopharynx was the same as that causing the peritonitis. In 2 instances the organisms were isolated from the nasopharynx 47 and 69 days, respectively, before peritonitis developed. In the cases of the 2 children who recovered, the organisms were isolated from the nasopharynx 17 and 77 days, respectively, after the termination of the peritonitis.

Treatment—A preliminary report is made by C. A. Aldrich, J. Stokes, Jr., W. P. Killingsworth and A. C. McGummiss¹¹⁷ of the use of *concentrated (lyophile) human blood serum* as a diuretic in the treatment of nephrosis. In the earlier cases the lyophile serum was dissolved in one-fourth of its original volume of distilled water. Later it was found that the same amount of compatible blood serum would dissolve the powder so that a concentration of 5 times was employed. The concentrated serum was injected slowly, not more than 5 cc. a minute. When a reaction occurred with the first dose of serum, all subsequent injections contained from 3 to 5 minims of solution of 1:1000 *epinephrine hydrochloride*. Caution must be exercised to prevent this concentrated serum from escaping into the tissues, since it is quite painful, causing rapid and intense swelling at the site of injection. No necrosis or slough, however, was noted at the site where the serum was accidentally injected into the tissues. The authors are not certain of the exact dose to be employed but have been inclined toward frequent small injections. In this series not more than 80 cc. or the equivalent of about 320 cc. of normal serum were given. Mild febrile reactions of short duration occurred in some instances. In 6 of 9 pa-

tients with typical lipoid nephrosis who were treated in this manner during their edematous phases, complete and immediate diuresis took place. Delayed and incomplete diuresis occurred in 1 patient. In 2 patients no beneficial results were noted. The authors intend to pursue this investigation and there will probably be further reports.

Since the introduction of *acacia* for the symptomatic treatment of nephrotic edema by Hartman in 1933, there have been several reports indicating that this method of treatment is not entirely without danger, particularly if it were continued over a long period of time. In view of the latter reports, the observations of E. M. Landis¹¹⁸ are of interest, although his data are based on observations in adults. Landis administered acacia in repeated daily doses of not more than 30 Gm. to 6 patients with nephrotic edema, the total dosage being 180 Gm. or less. In combination with a low fluid intake and rigid salt restriction, acacia produced a satisfactory diuresis in 5 of the 6 patients. In 1 patient, while acacia *per se* failed to induce diuresis, it did apparently increase the effectiveness of the *theophylline with ethylene diamine*, U. S. P. as a diuretic. Repeated Addis counts of the urinary sediment were made before, during and after the administration of acacia. No beneficial or deleterious action of this substance on the underlying renal lesion was observed. No change in blood pressure or any dangerous increase in blood volumes were observed with these small daily doses of acacia. The author believes that although the diuretic effect is only symptomatic and temporary, acacia is useful in treating persistent nephrotic edema in patients with marked hypoproteinemia, provided renal insufficiency, hypertension and cardiac failure are not complicating factors. It is recommended

that the ordinary diuretic drugs should be given a trial before acacia is employed, and acacia should be reserved for persistent, severe nephrotic edema that has resisted other therapy. It is advised that patients should be tested carefully for sensitivity to acacia before it is administered and the total dose should be kept below the level at which marked deposition in tissue occurs.

What may prove to be a rational manner of employing acacia in the treatment of the nephrotic syndrome is reported by S. A. Shelburne.¹¹⁹ Acacia is employed only at the beginning of treatment as a temporary measure for the elimination of edema and a *diet extremely high in animal protein* is provided immediately. In the 3 cases which the author reports, and in which acacia was employed only during the first few weeks, edema has not returned in any of the 3 over a period of observation of from 1 to 3 years. None of the patients were infants and the author doubts that this regimen can be adapted to the treatment of infants. In the case of a boy, 8 years of age, acacia solution (30 Gm. in 200 cc of water) was administered on 4 different occasions during a period of 13 days. In this period of time there was a total loss of body weight of 24 pounds. This represented 31 per cent of the total body weight.

M. J. Lepore,¹²⁰ whose experience has been with adults, also states that acacia has a definite place in the therapy of properly selected cases of nephrotic edema. He advises a previous trial on a high protein, salt-poor diet and the administration of such diuretics as *urea* or members of the saline diuretic group. These therapeutic measures may also be supplemented by others aimed at increasing the plasma volume and plasma proteins, for example, *transfusions of whole blood, serum or plasma*. If

these measures fail, the author then advises acacia therapy. Should an untoward reaction occur, the administration of acacia should be discontinued. He advises the administration of relatively small amounts of acacia. For adults this constitutes 500 cc. of 6 per cent acacia in normal saline. This is repeated at daily intervals for 3 or 4 days. If no diuresis results from this amount, there is apparently not much point in further administration. It is advised that the plasma albumin level should be watched closely and, if it falls too sharply, acacia therapy should be discontinued until the albumin level has been substantially improved. Lepore is inclined to disagree with Dick and his coworkers who believe that the decrease in plasma protein concentration which they observed was due to the toxic effect of the acacia. Lepore suggests that this was due in part to hemodilution and possibly in some instances to increased glomerular filtration, but not to any toxic action of the acacia on the glomeruli.

A. Goudsmit¹²¹ also reports good results with intravenous administration of acacia for the relief of the nephrotic type of edema. The administration of diuretics was of no effect until after the injection of about 2 Gm. of acacia per kg. of body weight. It was felt that acacia, by raising the osmotic pressure of the serum, was able to modify the physicochemical equilibrium in the body in such a way that diuretics became effective.

Some success in the treatment of nephrosis with *alkali* is reported by F. W. Schlutz and J. L. Collier.¹²² This form of treatment has been advocated by Osman in nephritis in which there is edema, marked albuminuria and low urinary volume. The acute or chronic parenchymatous or nephrotic type of renal disease with little or no structural impairment of the kidneys offers the most

suitable case for this form of treatment. However, it also appears to be useful in the treatment of mixed forms in which there is considerable structural damage and oliguria and edema with low plasma bicarbonate level. It is least effective in the chronic interstitial forms with hypertension, although even in these cases it may give some relief from excessive edema if the plasma bicarbonate level can be raised.

It is important to know the plasma bicarbonate level before beginning treatment with alkalis. The greatest benefit from alkalis is secured when they are given in amounts sufficient to raise the plasma bicarbonate to a normal level and to maintain it at that point. In favorable cases a marked diuresis and reduction of edema will occur when this point is reached. The output of albumin is generally greatly reduced, and it may in time completely disappear. While this form of treatment in no way restores a structurally damaged kidney or deters a process operating to that end, it may be expected with confidence that there will be marked relief from such distressing symptoms as excessive edema, oliguria, anuria and excessive proteinuria.

The dosages employed are frequently quite high and not entirely without danger. Overdosage should be guarded against by a periodic checking of the plasma bicarbonate. The alkaline salts are given by mouth until the plasma bicarbonate reaches a normal value or in the absence of untoward symptoms, they may be given even beyond this point. Confinement to bed is essential except in the mildest case, and the treatment is best carried out under hospital management. Except in the presence of oliguria or hematuria, an ordinary mixed diet without restriction of protein or salt may be permitted. No excessive restriction of fluid need be enforced, although

the fluid intake should not greatly exceed the fluid output. The alkalis are given in the form of *potassium citrate*, *potassium bicarbonate*, *sodium citrate* and *sodium bicarbonate*, generally in equal quantities. Water is added as well as a flavoring agent to disguise the taste. The potassium salts are more effective in reducing edema and promoting diuresis than are the sodium salts, but the former are more dangerous on account of possible toxic action on the heart. The sodium salts, though less powerful, have much the same action. If used alone, they cause more initial increase of edema than if used in combination with the potassium salts. All the salts may cause some unfavorable effects, the bicarbonate tends to cause nausea and vomiting and the citrates often produce alarming diarrhea, especially in children. For children the initial dose of the 4 alkalis in equal mixture is from 30 to 50 grams (2 to 3 Gm.) 3 times a day. The following day this amount is given 4 times a day or a total of from 120 to 200 grams (8 to 12 Gm.). Thereafter the dose is increased by 30 to 45 grams (2 or 3 Gm.) per day, until the pH of the urine is from 7 to 7.6. Dosages of from 500 to 800 grams (30 to 40 Gm.) a day and even higher, may be reached with safety. The weight generally increases at first and an extremely marked, and even alarming, initial increase of edema is practically a constant feature. Estimation of the plasma bicarbonate at frequent intervals is necessary at this stage. In spite of the marked increase of the edema, it is stated that it is necessary to increase the dosage of alkali fearlessly until the plasma bicarbonate reaches a normal level, or beyond, and to maintain the dosage continually high for some time, unless symptoms of toxic alkalosis, such as tetany, heart weakness or excessive

diarrhea or vomiting make a diminution of the dose, especially of the potassium salts, imperative. A remarkable diuresis is said to begin shortly after the height of the dosage has been reached; the pH of the urine is between 7.6 and 8.3 and the plasma bicarbonate is at normal level or above. The diuresis usually continues and often in an amazingly brief time results in complete loss of edema, marked diminution or complete disappearance of albumin from the urine and great reduction in lipemia. After the urinary volume has returned to normal a gradual reduction in the amount of alkali may be made. If there is any return of symptoms, the maximum dose must be resumed for at least a few days. A substantial dose of alkali should be continued for a considerable period after all edema has disappeared and the urine has cleared entirely of albumin, in order to insure against the return of active symptoms.

Two instances of sudden death following the intravenous injection of a mercurial diuretic are reported by H. M. Greenwald and S. Jacobson¹²³. In the case of 1 infant, 1 cc of neptal was administered intramuscularly 7 days before it was given intravenously. One minute after the intravenous injection, the infant became dyspneic and cyanotic, the pupils became widely dilated, the pulse imperceptible, and the child died. The authors are inclined to believe that the death was anaphylactoid in nature.

Although they state that neptal is not an antigen, yet, when injected intramuscularly, contact with the local issues may bring about the formation of a conjugate antigen with the body's own proteins, thus sensitizing the individual. Since the intravenous injection was given 7 days after the intramuscular injection, they believe it may have acted as the shocking dose. The second child was given 3 intravenous injections of neptal at 6- and

3-day intervals, respectively. The child died within 5 minutes after the third injection. Within 2 minutes there were convulsions, coma, cyanosis, and stertorous breathing.

The authors do not recommend that such mercurial diuretics as neptal or salyrgan be abandoned as a method of treatment for the elimination of edema in nephrosis. However, they do emphasize that, if the intramuscular route is employed, it be used exclusively and not changed subsequently to the intravenous route. They also advise caution in regard to the size of the dose employed, recommending an initial small dose and, if no unusual symptoms and signs appear, such as chills, elevation of temperature, malaise, morbilliform rash, headache, vomiting, or convulsive seizures, to increase the dose gradually. These manifestations must be considered as danger signals and contraindications to the subsequent administration of the drugs.

Renal Rickets

Contrary to the experience of most observers, G. Graham and W. G. Oakley¹²⁴ report some degree of success in the treatment of renal rickets. Two children with this syndrome were treated with sufficient *alkali* to restore the alkali reserve to within normal limits, and at the same time with large doses of *vitamins D and A*. The general condition was improved, there was a gain in height and weight, the condition of the bones was greatly improved, there was slight improvement of kidney function and but little change in the degree of anemia. The amount of alkali given was the equivalent of from 3 to 5 drams (12 to 20 Gm) of sodium bicarbonate daily (20 grains or 1.3 Gm each of magnesium oxide and sodium bicarbonate 3 times a day is equivalent to 5 drams or 20 Gm of sodium bicarbonate). Both children

died, 1 apparently of the kidney condition, the other of an intercurrent gastric disturbance.

Vulvovaginitis

The importance of infection of the lower part of the genital tract in girls as a clinical and sociologic problem is emphasized by J. L. Reichert, I. M. Epstein, R. Jung and C. A. Colwell.¹²⁵ They have observed 121 girls with such infections, 76.6 per cent of whom had gonorrheal infections and 23.4 per cent nonspecific ones. The vulva was always involved, the cervix almost always and the urethra in about one-half of the cases of gonorrhea and one-fourth of the cases of nonspecific infection. The vagina was involved in 41 per cent of the cases of gonorrhea and in 19 per cent of the cases of nonspecific infection. Vaginitis occurred usually only in the acute stage. No instance of gonorrheal proctitis was found.

No qualitative clinical distribution was found between the gonorrheal and the nonspecific infections. The final differential diagnosis was based entirely upon the examination of smears and cultures. Urethral smears were taken with cotton rolled to a point on a toothpick. It was found that the urethra could be entered for a distance of from 3 to 4 mm without the child's feeling discomfort. When pus is scanty, it is necessary that smears be taken from the cervix and the urethra. For a cervical smear, the child should be in the dorsal lithotomy position, the labia minora separated to the point of opening the vaginal orifice and a sterile applicator introduced with a spiral motion to keep the hymen from adhering to the cotton. The applicator is allowed to assume its own direction and is introduced, with a spiral motion and with a minimum of pressure, until resistance is encountered. The tip of the applicator

is then in the posterior fornix. By depressing the distal end, the tip is lifted over the cervix. It is rolled so that the cotton is wiped over the cervix and is then withdrawn.

When cervical secretion was desired for culture, they employed the following method: After material was obtained from the external genitalia, the vulva was washed with soap and water and dried with sterile gauze. A sterile Number 30 Kelly endoscope was inserted just into the vagina. An endoscope of this size fits the introitus tightly enough to seal the opening of the vagina. The obturator was then removed and an airtight window and side arm were fitted on the endoscope. The vagina was then inflated under inspection to the point at which the vaginal walls were separated sufficiently to allow the endoscope to be passed in just short of the cervix without touching the vaginal mucosa. The window was then removed, and a fitted sterile tube was passed through the endoscope to the cervical os. Through this inner tube was passed a small glass pipette, with its point carefully rounded, which was connected with a rubber bulb for suction. Even when there was only a little secretion at the cervix, a few drops could usually be obtained by this method. If the amount of material was insufficient, from 0.5 to 1.0 cc. sterile, warm, distilled water, adjusted to a pH of 7 was first introduced through the pipette.

It is pointed out that smears and cultures are both necessary in the determination of an accurate diagnosis of gonorrhea, and that neither is adequate alone.

Treatment—Two per cent *strong protein silver* in tragacanth jelly was found to be the most effective germicide. In the cases of gonorrhea, it resulted in an apparent cure in 80 per cent of the cases in 1.5 months. There were

recurrences in 10 per cent. The average duration and treatment in the cases of nonspecific infection was 1 33 months, with apparent cure in all cases.

The group of patients treated with **estrogen** were apparently cured in a shorter time than was the group which received local treatment; there was, however, a higher incidence of exacerbations in the estrogen group. In all girls showing an unsatisfactory response to treatment with estrogen, there was a persistent or recurrent cervicitis. Local treatment following the treatment with estrogen resulted in a permanent cure in about 1 month in these patients. They also found that the use of **theelin suppositories** tended to a reduction in the total amount of estrogen necessary to effect a cure.

An unusual high degree of success in the treatment of gonococcal vaginitis with the estrogenic hormones has been reported by R. W. Te Linde.¹²⁶ All of the 175 children treated with **amniotin** are reported as cured. All, except 16 of those to whom the product was given hypodermically in oil, were cured by the use of amniotin vaginal suppositories. The author states that he has yet to encounter a patient who failed to get well by this method of treatment. A follow-up of the first 100 patients from 3 months to 2½ years after the last treatment, showed 98 of them well. So far they have found no clinical evidence of harm from this treatment. While they feel that the increased acidity brought about in the vagina by the action of the estrogen is a factor in overcoming the infection, they believe that amniotin introduces an additional factor, since their results were not nearly so good when another acidifying suppository was employed. They are inclined to believe that this other factor is the covering of the vagina with thick epithelium, which prevents reinfection of the subepithelial tissues and

thus permits the inflammatory process in them to subside. Their clinical observations as well as examination of biopsies indicate that the essential lesion of gonococcal infection of the lower part of the genital tract in female children is vaginitis.

Encouraging results in the treatment of vaginitis in children with **silver picrate suppositories** is reported by A. J. Kobak and L. E. Frankenthal, Jr.¹²⁷ Their method of treatment was as follows: At each visit the cervix and vagina were examined through an infant vaginoscope and a smear was taken from the vaginal portion of the cervix. The mother of the patient was instructed to cleanse the vulva between the labial folds daily or more often with a soft cloth and to use bland soap such as castile or superfatted types. Suppositories of sufficient length to occupy the entire length of the vagina were given to the mother with instructions for their insertion. The suppository had a boroglycerine gelatin base. Each one contained 1 gram of silver picrate. A suppository was inserted each night just before bed time except in the evening before the day of the next visit to the clinic when it was omitted. Daily treatment was administered by the mother until the discharge and signs of inflammation disappeared and the smears became negative. Then the treatment was gradually spread out until the patient was receiving no local treatment and merely returned for purposes of smear examination.

Five of the patients had a permanent negative smear after 1 week of treatment and 3 became negative at 3 weeks. Four patients became permanently negative after 6 to 9 visits to the clinic. Only 1 patient remained resistant to treatment and did not become permanently negative until 15 clinic visits had been made.

Sulfanilamide in the treatment of gonorrheal vaginitis has been employed in a series of 25 girls by S. J. Hoffmann, M. Schneider, M. L. Blatt and R. D. Herrold.¹²⁸ Of these, 7 were cured in an average of 17 days and 9 in an average of 43 days. Only 2 of the remaining patients were cured by additional administration of sulfanilamide. A standard dose of sulfanilamide was used in all instances. Their procedure was as follows: During the first 2 days the daily dosage was 3.4 grains (0.05 Gm) per pound of body weight in 4 equally divided doses at intervals of 6 hours. During the next 5 days the dosage was reduced to three-fourths of this amount, or $\frac{3}{16}$ grain (0.4 Gm) per pound daily. During the second and third week, the dosage was reduced to $\frac{3}{8}$ grain (0.025 Gm) per pound daily or one-half the initial dosage. At the end of a 3 weeks' course of treatment a rest period of 1 week was given regardless of the results as shown by smear

examinations. All patients with smears which were positive at the end of this rest period were given a second course exactly like the first. A rest period was also given at the end of the second course of treatment and for the majority of patients who were still infected at the end of the second rest period, a third course of treatment was administered. A few patients were given a fourth course of treatment after the third rest period.

A clinical study to determine the efficacy of sulfanilamide in the treatment of gonococcal vaginitis in children has also been carried out by J. W. Holmes, J. A. Jones, and N. Gildersleeve.¹²⁹ The drug was administered in doses of 10 grains per 20 pounds (66 mg. per kg) of body weight per day. No untoward effects were noted. However, their experience would indicate that sulfanilamide, either by oral administration in the above dosages, or in suppositories, is of no particular value in the treatment of gonococcal vaginitis in children.

HEART DISEASE IN CHILDREN

BY ROBERT A. LYON, M.D.

Bacterial Endocarditis

Bacterial endocarditis in a 15-year-old child, due to a hemolytic parainfluenzal bacillus, has been described by J. A. Lichty, Jr.¹³⁰ The bacillus occurred in the circulatory system and was also obtained from the discharge of the nasopharynx which was suspected of being the portal of entry of the organism. Seven other patients with this type of subacute bacterial endocarditis have been described in the literature and in all cases the infection lasted for 5 to 10 weeks before the death of the patient. A past history of heart disease occurred in only one-half of the group and 4 of the 8

patients were under 15 years of age. It was suggested that artificially induced fever might aid in the treatment of this disease.

In rare instances, endocarditis may occur in early infancy. Four such cases have been reported by R. Feldman.¹³¹ One infant, 13 months of age, had a myocarditis with parietal endocarditis following a streptococcus septicemia. Another patient, who had several deformities of heart structure, died of pneumonia at the age of 6 months and a progressive endocarditis of the pulmonary and mitral valves was noted at autopsy. Another child, 7 months of

age, had a subacute bacterial endocarditis following pharyngitis, otitis media and tracheobronchitis. The fourth infant, 4 months of age, had an endocarditis of the mitral valve with a very large heart. The mother of this patient had had rheumatic fever during her pregnancy and the infant's cardiac disease was thought to have been acquired during fetal life or during the first few months after birth.

Cardiac Hypertrophy

Cardiac hypertrophy in infancy has been reviewed from a pathological standpoint by H. E. McMahon.¹³² He was able to group the autopsy findings into 3 general classifications: (a) The cases in which the cardiac enlargement was due to true hypertrophy of cardiac muscle fibers; (b) the cases in which the muscle fibers became swollen with deposits of glycogen, and (c) the cases in which there was an increase in the amount of connective tissue in association with myocardial fibrosis. The author called especial attention to the first type of true muscular hypertrophy which has not been described previously in the medical literature. He had observed 1 patient, 6 months of age, who had a congenital abnormality of the urinary tract and definite enlargement of the heart. There was histological evidence that the cardiac muscle fibers were in an active state of growth and a large number of mitotic figures were present. Lesions which cause extra work on the part of the heart, such as coarctation of the aorta and hypertension, might well cause hypertrophy of the muscle fibers of the heart and this possible cause of cardiac hypertrophy should always be considered.

Cardiac enlargement associated with dietary deficiencies has been noted in a series of 13 children by J. I. Waring.¹³³

All but 1 of the children were negroes and their ages varied from 14 to 48 months. No evidence of scurvy or rickets could be found in any of the patients but the protein levels of 3 of 8 of the total group were diminished with a change in the albumin-globulin ratios characteristic of nutritional edema. A series of 34 other patients with nutritional edema did not show evidence of cardiac enlargement. Although no definite deficiency of vitamin B₁ was detected in the children with cardiac enlargement, the early treatment of the condition with adequate diets with added vitamin concentrates caused a slow return of the heart size to normal proportions.

Chorea

In a study of the relationship of chorea to other rheumatic infections, a series of 467 patients were reviewed by L. P. Sutton and K. G. Dodge.¹³⁴ Emotional disturbances preceded the chorea attacks in about 9 per cent of patients, rheumatic episodes in 9 to 14 per cent, other infections in 5 to 8 per cent and no evident disturbance in 69 to 77 per cent of cases. Only about 20 per cent had chorea alone, the remainder developing joint pains or other rheumatic manifestations. In the 91 patients with pure chorea, heart lesions developed in about 20 per cent over a period of observation of approximately 5 years. In those with other associated rheumatic symptoms, heart lesions occurred in 73 per cent. In 50 per cent of the number of patients whose first manifestation of rheumatic fever was chorea, other lesions of the syndrome such as joint pains developed so that the authors concluded that chorea should still be considered as a manifestation of rheumatic fever.

In the analysis of 78 cases of chorea without other rheumatic symptoms, P. L.

Parrish, L. M. Taran and S. Starr¹³⁵ found a higher incidence of carditis than has been reported recently from other clinics. More than a third of the patients had definite evidence of heart involvement. Following roentgenologic examination, an additional number were suspected of having cardiac lesions. Only 8 per cent of the group were entirely free from heart disease. Children with chorea and other rheumatic symptoms developed cardiac disease in 67 per cent of cases with an additional number giving roentgenologic evidence of heart involvement. The authors believed that chorea should still be classified as a part of the rheumatic syndrome and that heart lesions may be expected to follow in a relative high percentage of cases.

Obesity has been mentioned as a *complication of chorea*. Two such cases have been reported recently by P. R. Evans.¹³⁶ Both of the patients were girls, one 9 years of age and the other 6 years of age, at the time of the first attack of chorea. During the 2 or 3 years following chorea, rapid gains in weight occurred so that by the age of 11 years both children were definitely obese. There was no definite evidence of dysfunction of the pituitary gland. The administration of *thyroid extract* caused a considerable reduction in the weight of both patients but it terminated in the development of recurrences of chorea so that this therapy was discontinued and dietary measures alone were employed. These 2 patients occurred in a group of 27 chorea patients. The remainder of the children were not obese although 8 were above the expected weight for their age and 4 of these were gaining more rapidly than would be expected. In the previous medical literature are reports of 11 patients with obesity developing after attacks of chorea. It has been supposed that the

lesions causing chorea may also involve parts of the central nervous system or other organs of the body which regulate metabolism or weight gain.

Treatment—Favorable results from the *artificial fever therapy* of chorea have been reported by C. H. Barnacle, J. R. Ewalt and F. G. Ebaugh.¹³⁷ Daily treatments with the Kettering hypertherm were given to 45 children until their body temperatures were raised to 105° F. (40.5° C.) for a period of 2½ hours. Of the total group, 37 recovered completely and 8 were greatly improved by the treatment. In a follow-up study of 44 patients it was found that 36 had remained well, 4 had had recurrences and the remaining 4 had shown marked improvement of their symptoms. The average number of treatments was slightly more than 12 and the duration of the therapy was 22 days as an average. None of the children had lost their appetites or had any diminution of weight. Delirium occurred 12 times during a series of 562 treatments but the authors did not consider the treatment to be injurious and found no reason to believe that advanced rheumatic carditis was any contraindication to the therapy.

Fever therapy was found to be satisfactory in the treatment of the chorea patients observed by L. Speker and A. McBryde.¹³⁸ Of a total of 8 children, 5 responded well with a rapid subsidence of symptoms. One other was moderately improved and the remaining 2 did not respond with elevations of temperature. The fever was induced by radiant energy from 7 120-watt bulbs in a cellotex-lined box. The authors could see no advantage in this method of inducing fever over the treatment with typhoid vaccine, which was easier to administer and produced similar results.

The experience of various clinics with artificial fever therapy has been reviewed recently by H. W. Kendell and W. M. Simpson.¹³⁹ Expressions of approval have come from different parts of the country and the authors added a report of 5 patients of their own who benefited by the therapy. The ages of these children ranged from 11 to 14 years and 1 to 11 treatments were needed to produce adequate results. The duration of the illness seemed to have been shortened, and no recurrences were noted during a period of 6 weeks to 4½ years of observation. Three patients had carditis and these as well as the other 2 children had no complications from the treatment.

In a follow-up study of 99 chorea patients who had received fever therapy, L. P. Sutton and K. G. Dodge¹⁴⁰ found that the progress had been materially better than that of an untreated control group. One series of 48 treated patients who had been observed for 1 to 3 years was compared with a group of 23 untreated patients. A second series of 51 treated patients was compared with a group of 37 untreated ones who had been observed for 4 to 6 years. Heart disease, attacks of chorea and polyarthritides, and the deaths, were considerably less frequent in the treated groups of patients. The most marked differences between the 2 groups were the higher percentages of polyarthritides and deaths from heart disease in the untreated series. Further analysis of the heart disease in the 2 groups showed that although the incidence of cardiac lesions was not greatly different in the 2 series, the severity and extension of the pathological changes was much more marked in the untreated patients.

A fatal result from the use of fever therapy has been recorded recently by E. Friedman and C. J. Stettheimer.¹⁴¹

A girl, 2½ years of age, who was suffering from gonorrheal vaginitis developed a circulatory collapse and exhaustion after the first treatment with fever produced by an electrical inductotherm, and died within a few hours. Several other patients under their observation had suffered rather severely from the treatment and they believed that the dangers of any therapy of this sort should be thoroughly understood by the clinician before it is recommended.

Congenital Heart Disease

Congenital heart disease was found in 105 instances of a total series of 1950 autopsies of children, by S. Gibson and W. M. Clifton.¹⁴² There were no differences in sex incidence but the cardiac lesions were more numerous in the younger children. In 24 patients there had been no clinical evidence of the cardiac anomaly. Arteriovenous shunt occurred in 65 patients and the most common lesion of this group was an auricular septal defect in 24 instances, while patent ductus arteriosus occurred in 17 and interventricular defects in 12. Combinations of these lesions were noted in the remainder of the group. Clinical symptoms of the auricular defects were usually absent although a systolic murmur was noted in a few cases. Patency of the interventricular septum was diagnosed before death by the presence of a harsh systolic murmur heard best in the third interspace. The typical murmurs of a patent ductus arteriosus were frequently absent or limited to the systolic phase in younger patients. In only 1 instance of the group of 17 patients was the typical humming top murmur heard, and that in a boy 11 years of age. In patients with an arteriovenous shunt, other lesions occurred frequently, and consisted chiefly of partial transposition of the great vessels and the tetralogy of Fallot.

In 7 patients, mongolism accompanied the congenital heart disease, and in 28 instances (27 per cent) other congenital anomalies occurred elsewhere in the body.

In a review of the subject of congenital heart disease, T. J. Dry¹⁴³ has listed the *abnormal findings* which would lead one to suspect such cardiac abnormalities. The symptoms included bruits, and thrills not accounted for by acquired lesions, which are most frequently noted in infancy and remain fairly constant over a period of years. Cyanosis, polycythemia, clubbed fingers and toes usually indicate venous-arterial shunt. Congenital heart disease may be suggested by unusual cardiac contours in the roentgenogram, especially such abnormalities as the prominence of the pulmonary artery, a lack of prominence of the aortic knob, shadows to the right of the sternum running up towards the right sternoclavicular joint (indicative of persistent right aortic arch) and erosion of the ribs (coarctation of the aorta). Hypertension in young adults, congenital anomalies of the patient elsewhere in the body and subacute bacterial endocarditis lead one to search for congenital heart disease. The electrocardiogram will indicate dextrocardia with complete situs transversus but otherwise it rarely demonstrates any of the lesions of congenital heart disease, but may assist in the determination of the nature of the lesion. Fourth lead records may also assist with the diagnosis but produce no evidence pathognomonic of congenital lesions. The prognosis of certain lesions such as uncomplicated septal defects, patent ductus arteriosus, subaortic stenosis, and persistent right aortic arch is generally good except for the possibility of occurrence of subacute bacterial endocarditis.

An apparent increase in the blood velocity rate may result from the right to left shunt of blood in the hearts of patients with septal defects. The sodium cyanide test employed by J. McGuire and F. Goldman¹⁴⁴ in 11 normal patients indicated that the normal time for the circulation of the drug was 10.6 seconds, varying between 9.0 and 14.5 seconds. In 5 children with cyanosis, the rates averaged 12.1 seconds. In 3 patients with a clinical diagnosis of right to left shunt, probably due to the tetralogy of Fallot, the rates were 3.8 to 4.8 seconds. In 2 other such patients no reactions occurred and the rate of blood flow could not be measured. The authors concluded that this test of blood flow velocity might be helpful in the diagnosis of doubtful cases of right to left shunt in congenital heart disease.

Complete *interruption of the aortic isthmus* with transposition of the great arteries was noted in an infant, 3 weeks of age, by L. P. Hamburger, Jr.¹⁴⁵ Clinical symptoms were deep cyanosis of the upper extremities extending to the level just below the umbilicus and less cyanosis of the legs, strong pulsation in the legs and arms, roentgenologic evidence of cardiac enlargement with a narrow aortic shadow and no pulmonary conus, and finally an electrocardiographic tracing showing a T-wave of low amplitude in Lead I. At autopsy, it was noted that the aorta arose from the right ventricle, gave rise to the innominate, left carotid and subclavian vessels and then was occluded. From the left ventricle came a vessel which gave off the 2 pulmonary arteries and continued as the descending aorta. The pulmonary veins emptied into the left auricle. Thirteen instances of complete atresia of the aorta have been reported in the literature previously but in only

1 other was there a transposition of vessels.

The *incidence of organic heart disease* among pupils of San Francisco schools has been found to be 0.37 per cent, by J. J. Sampson, A. Christie and J. C. Geiger.¹⁴⁶ The same percentage was noted in a diagnostic clinic and in a sample of about 13,000 school population. More than half of the clinic patients and slightly more than a third of the school sample with organic heart disease owed the condition to congenital lesions which indicated a relatively low incidence of rheumatic heart disease. No differences occurred in the sex distribution, and the incidence of the rheumatic heart disease was greatest in children 13 to 15 years of age.

Hypertension

A study of a group of children with elevated blood pressures by H. B. Tausig and M. S. Hecht¹⁴⁷ seemed to indicate that rheumatic fever might be an etiologic factor. Diastolic pressures above 90 were considered as evidence of hypertension. In a series of 37 children with this condition, no cause for the hypertension could be discovered other than a prolonged infection with 1 of the manifestations of the rheumatic syndrome. In another series of 12 rheumatic patients the blood pressure readings varied over wide limits and the significance of the elevation could not be determined except that these children also had the common background of rheumatic infection. In all of the 49 children, there was a tendency for the hypertension to occur after the age of 10 years and with the onset of puberty. At this period hypertension has been observed with considerable frequency in normal children but any such case seemed worthy of repeated observation with the chance that rheumatic fever could act

as an etiologic or contributing factor in producing a permanent elevation of blood pressure

Cardiac Complications of Acute Hemorrhagic Nephritis

The cardiac complications associated with acute hemorrhagic nephritis have been reviewed by M. I. Rubin and M. Rapoport.¹¹⁴ In a series of 55 patients with nephritis, 14 showed some evidence of myocardial damage. It was questionable whether the toxic or infectious process which was demonstrable in the kidneys may have produced similar changes in the heart muscle or whether the accompanying hypertension caused mechanical strain on the myocardium. Autopsies on patients with nephritis have demonstrated myocardial changes in some instances.

In the patients observed by the authors there was no direct relationship between the amount of cardiac damage and the severity of the nephritis nor was there any difference in the duration or outcome of the nephritis in patients who showed cardiac involvement and those who did not. In 2 instances the patients died during the course of nephritis with symptoms of acute heart failure. All but 1 of the nephritic children recovered from their nephritis and had no residual evidence of heart disease. One patient, who had evidence of some permanent cardiac damage, also had a chronic hemorrhagic nephritis.

Treatment—The treatment of nephritis patients with heart involvement differed somewhat from the routine therapy of nephritis alone. Intramuscular injections of *magnesium sulfate* solutions, and *digitalization* seemed to be especially indicated in the cardiac patients. *Morphine and oxygen* were employed freely when severe cardiac failure occurred. The amount of fluid allowed was

made dependent upon the degree of hypertension and the amount of cardiac involvement present. As a rule, the fluid intake was limited to 750 to 1000 cc. daily when the blood pressure was elevated.

Paroxysmal Tachycardia

Paroxysmal tachycardia in a newborn infant has been reported by L. M. Taran and K. G. Jennings.¹⁴⁸ The rapid heart rate of 250 to 300 per minute developed on the eighth day after a difficult delivery by version. The tachycardia was nodal in origin and vagal stimulation by reflex methods or by drugs seemed to have no effect on the rate. The administration of digitalis in the form of digifolin gave the best results in reducing the rate to more normal figures and in re-establishing a normal rhythm. The patient recovered and was in good health at 23 months of age. In a review of the previous literature the authors found that 52 cases of paroxysmal tachycardia had been reported in children between the ages of 4 days and 15 years, with no significant age or sex distribution. Congenital heart disease and infections such as measles and pertussis seemed to be possible predisposing causes. The most frequent symptoms of the condition were dyspnea, cyanosis and cardiac dilatation and the arrhythmia was more frequently auricular than nodal or ventricular in origin.

Pericarditis

Pericarditis occurring in an infant 3 weeks of age has been observed by J. Wolff.¹⁴⁹ After an operation for pyloric stenosis the infant developed pneumonia and empyema. Pericardial fluid was detected before death and autopsy showed the presence of pericarditis. In previous cases, pericarditis following septic diseases had been noted, and the important clinical manifestations were a softening

and impurity of both heart sounds, associated with other evidence of cardiac failure such as cyanosis and liver enlargement.

A diagnostic sign of acute fibrinous pericarditis, consisting of a high pitched murmur of a bleating quality has been noted by M. M. Mahner.¹⁵⁰ The murmur seemed loudest in the apical region where it displaced the systolic endocardial murmur and was transmitted to the axilla. There was a tendency for this squeaking murmur to appear and disappear at intervals. In 12 children 3 to 11 years of age, this murmur was noted from 2 weeks to 2 years before the friction rub occurred or the signs of pericardial effusion developed. The mortality of this series of 12 patients was high (33 per cent) and it seemed likely that the occurrence of this type of murmur representing fibrinous pericarditis was of grave prognostic significance.

Psychological Effect of Heart Disease

The psychological effect of heart disease on children of adolescent age has been the subject of a report by H. B. Silver.¹⁵¹ He selected for study a group of 21 girls between the ages of 12 and 18 years who were residing in an institution. They had cardiac lesions of varying severity but the great majority were able to lead fairly active lives without any distress and their intelligence levels were within the normal range. The methods of investigation included a complete social service history, interviews with the parents and children separately and objective tests such as "The Adjustment Inventory" of Bell and the "Personality Schedule" of Thurstone. The author concluded that the presence of the heart disease in this group of girls had not had any adverse effect on their conduct or social adjustment. Factors which

might produce such difficulties seemed to be the sense of guilt developed by many parents because of their children's affliction and because of their fear of the cardiac condition so that they tended to set up overprotective measures for the children. Institutional life apparently helped to eradicate abnormal conduct of the patients and provided for them a means of proper adjustment.

Rheumatic Fever

Course and Prognosis—The outstanding characteristics of 306 children and young adults with rheumatic fever who have died have been studied by E. F. Bland and T. D. Jones.¹⁵² No patient whose rheumatic fever developed after the age of 21 years has been included in the series, and most of the patients were 8 to 18 years old. Of the total group, 250 (82 per cent) died as the result of their rheumatic infections and the remainder from other causes. Autopsies were performed on 74 patients. In 94 per cent of the entire group, cardiac disease was present from the time of the onset of rheumatic symptoms. Death occurred within 5 years after the onset of the illness in 62 per cent of the patients but no relationship between severity of rheumatic fever and the age of onset could be found. A history of arthritis was common in this group of patients but it frequently was very mild in type and was a less prominent feature than abdominal or precordial pain in producing discomfort. Chorea was not a common preceding symptom and rheumatic nodules, although often found upon careful examination, seemed to have no bearing on the prognosis. Carditis, manifested by enlargement, murmurs and congestive failure, was the most constant finding. Pericarditis, evident from clinical findings in 35 per cent of a group of 135, was found at autopsy to be

present in acute forms in 55 per cent and in chronic or acute forms in 80 per cent. Electrocardiograms gave little prognostic help although, in this series, delay in conduction time was noted in 40 per cent of the group, and auricular fibrillation in 18 per cent. Pulmonary lesions occurred in 28 per cent and hepatic involvement was noted in every patient, which was manifested by destruction of hepatic cells, hemorrhagic areas and deposits of fibrin. These changes suggested the presence of a severe toxemia in addition to the acute congestion.

A decrease in the incidence and recurrence of rheumatic fever attacks at the age of puberty has been reported by M. Leonard.¹⁵³ A series of 500 patients were analyzed and 358 (71 per cent) were found to have developed heart lesions. Chorea, characteristic polyarthritis, subcutaneous nodules and active rheumatic heart disease were employed as criteria of rheumatic infection. The initial attacks occurred most frequently at ages of 5 to 11 years and there was a sharp drop in the rate of initial attacks and the development of heart disease at the ages of 13 to 15 years which was taken as the period of puberty. A group of 60 patients had 2 or more attacks but the recurrences in this series greatly diminished at the age of puberty. Further analysis of a group of 108 patients followed for 5 to 13 years indicated that the annual rate of recurrences over an age period of 7 to 17 years had fallen gradually. Rather than believe that children develop an immunity to rheumatic fever during adolescence, the author was inclined to believe that secondary attacks usually follow closely upon the initial attack and a gradual decrease in susceptibility occurs with advancing age. The knowledge that improvement of rheumatic heart disease may occur at

puberty may be of value in the prognosis of the disease.

The prognosis of patients with mitral insufficiency or potential heart disease, has been reviewed by J. A. Boone and S. A. Levine.¹⁵⁴ They were able to observe 225 adolescents and young adults for an average period of 9.6 years. Only 8 patients of a group of 166 with potential heart disease developed permanent valvular lesions, and half of this number had had subsequent rheumatic attacks after the initial observation. Of the patients with mitral insufficiency at the time when they were first examined, 58 per cent remained unchanged, and 42 per cent developed mitral stenosis or aortic insufficiency. Patients with a history of chorea alone developed cardiac lesions in about 7 per cent of cases; those with rheumatic fever alone in about 10 per cent, and with combined infections in about 18 per cent. A small group of 10 patients with heart disease had no previous history of chorea or any other rheumatic symptoms.

Etiology—The manifestations of the rheumatic syndrome may be induced by other diseases. Less common among the reported predisposing infections of this type has been diphtheria. Five instances have been reported by H. G. Huber,¹⁵⁵ who observed chorea or arthritis develop immediately after attacks of diphtheria. Three children, 8 to 9 years of age, develop polyarthritis within 1 to 6 weeks after the onset of diphtheria. One had had a previous arthritis. Two other children, 10 to 13 years of age, developed chorea 11 to 13 weeks after the diphtheria infection. It was questionable whether the diphtheritic antitoxin had been responsible for the development of such rheumatic symptoms. Since not all of the patients had received this form of treatment and the interval between its administration and the occurrence of

joint pains and chorea was so long in many cases, the author was inclined to believe that the diphtheritic infection itself had provoked the rheumatic disease.

Blood cultures of a series of rheumatic patients yielded negative results in the investigation of C. J. Leslie and M. J. Spence.¹⁵⁶ The series included 22 patients with active rheumatic infections, 4 with chorea, 9 patients with other illnesses and 8 healthy individuals. Pathogenic bacteria were recovered from 1 rheumatic patient and from 1 of the healthy control patients but the evidence indicated that these microorganisms were contaminants. Various other bacteria were recovered after manipulation or subculture of the initial culture material but the authors concluded that there was no definite evidence of bacteremia in their series of patients.

Diagnosis—Considerable importance has been attached to *the intensity of the first heart sound* in relation to the conduction time in the diagnosis of heart disease in children by J. D. Keith.¹⁵⁷ A delay in the conduction time with a P-R interval of 0.18 second or more tended to cause a diminution in the intensity of the first heart sound. In 37 patients with first attacks of acute rheumatic fever all of whom had a prolonged conduction time, there was marked diminution in the intensity of the first sound, and sometimes the sound was almost inaudible. There was little relationship between the quality of the first sound and variation in the P-R intervals of less than 0.16 second. It must be borne in mind that certain other factors may diminish the intensity of the first sound, such as thickness of the chest wall, pulmonary emphysema, pericardial effusion, or myocardial damage, but most of these conditions are rare in children.

In another series of 25 patients who had had more than 1 attack of rheumatic fever and conduction times of 0.18 second or more, the first sound was very much diminished in intensity in all but 4 patients. The P-R interval could be predicted with a considerable degree of accuracy by the intensity of the first heart sound and the author believed that it was of more importance than the murmurs themselves. Since the first sound probably is valvular in origin, the intensity is produced by rapid changes in pressure between the ventricles and auricles causing the valves to snap shut quickly. Any delay in the conduction time within the heart probably allows slower changes in auriculoventricular pressures and the mitral and tricuspid valves are partly closed before ventricular systole begins so that the final closing of the valves produces a much diminished sound.

The importance of careful determination of *heart size* as a more valuable diagnostic sign than the cardiac murmur has been stressed by M. G. Wilson.^{15b} Transverse enlargement of the heart, determined by percussion or the roentgenogram, should be supplemented by roentgenologic examinations of oblique views of the heart. In only 65 per cent of patients with valvular lesions could enlargement be detected from frontal views only as compared with 100 per cent from oblique and frontal roentgenograms. In a group of 57 patients with congenital heart lesions, the murmurs changed in quality and transmission over a period of years but the cardiac silhouettes remained the same. In children with murmurs of doubtful significance (accidental or benign murmurs) regression of physical signs occurred in 36 per cent of instances but the roentgenologic examination of the

heart showed some abnormality in all but 5 patients.

In children with acquired heart disease, the murmurs were even more inconstant. Of a group of 179 children with murmurs of mitral insufficiency, changes in physical signs occurred in 89 per cent of cases, and in a series of 135 children with mitral stenosis, the murmurs changed from time to time in 46 per cent of cases. During this time cardiac enlargement was noted more constantly and in some patients the size and configuration were abnormal in some instances even though no characteristic murmurs were heard on physical examination.

The author concluded that roentgenologic examination should always be included as a routine procedure in the diagnosis of cardiac conditions and it is possible that cardiac lesions might be discovered in a larger number of children than could be detected from physical signs alone.

The *fourth lead electrocardiogram* in children has been found to be of some value by P. F. Dwan and M. J. Shapiro.^{15c} In a series of 72 children with rheumatic heart disease, myocardial damage could be demonstrated in 36 per cent of the patients by the 4 lead tracings and in only 29 per cent when the 3 conventional leads were employed. The fourth lead tracings of 33 children with congenital heart disease gave no more information than had been obtained from the ordinary 3 leads. Four lead electrocardiograms which were made daily for 10 days on 4 patients with subacute rheumatic heart disease, gave constant results from day to day. The standard technic for taking fourth lead tracings in which the right arm electrode is placed on the anterior part of the chest and the left arm electrode is placed on the back was compared with the

method in which the left arm electrode was placed on the leg instead of the back. The latter procedure is an easier method because it eliminates the difficulty of adjusting the electrode on the back of certain patients who are confined to bed but it seemed to be less accurate in a series of 8 patients because the tracings tended to assume the characteristics of the conventional leads. The authors urged that standard methods of obtaining fourth lead tracings be adopted so that the results of various clinics may lend themselves to more accurate comparisons.

Skin Lesions—A frequent skin manifestation of rheumatic fever is erythema marginatum or erythema annulare. C. B. Perry¹⁶⁰ believes that the eruption is specific of rheumatic disease. He has observed 13 such patients, all children under 16 years of age. The erythema was a less frequent manifestation than the subcutaneous nodules. The characteristics of the eruption were a circular design which tended to spread, leaving behind it areas of normal skin. The most usual sites were the abdomen and chest and it occasionally occurred on the limbs but rarely on the face. The eruption frequently appeared at the beginning of an attack of rheumatic fever but was noted at any time during the infection. As a rule, the rash appeared when the patient was making clinical improvement and it seemed to be a good prognostic sign.

The incidence of nodules in patients with rheumatic fever seems to vary in different parts of the United States and Europe. The figures collected by H. I. G. Anderson¹⁶¹ showed that in London they are observed in 10 to 50 per cent of such patients, and in New York City in 11 per cent. In his own series of 114 rheumatic children from North Carolina and Virginia, the author found nodules

in 9 instances and 2 others had had a history of such lesions, making a total incidence in that locality of about 10 per cent.

Treatment—A stock *filtrate of streptococcus hemolyticus* was employed in the treatment of 34 rheumatic children by V. P. Wasson.¹⁶² Injections of small amounts were given at first and were followed at weekly intervals with 12 doses of increasing potency. After this period of time doses of moderate size were administered each month. The following year the same treatment was repeated. In a series of 34 children with rheumatic infections, the course of the disease seemed milder, their general condition better and the recurrences and exacerbations of the disease were much less than those of a control group.

Not only did sulfanilamide produce no beneficial results in the children with rheumatic fever treated by B. F. Massell and F. D. Jones¹⁶³ but severe reactions occurred so frequently that the drug seemed to be *contraindicated*. The series of 58 patients included 16 moderately to severely ill children, 25 recent convalescents and 17 in inactive stages of the disease. Rashes and fever were the most frequent reactions which followed the administration of sulfanilamide in initial doses of 6 to 7 grams per 10 pounds (97 to 113 mg. per kg.) of body weight for the first 24 hours and 4 to 5 grams thereafter. The children with acute forms of the disease developed reactions more frequently than the quiescent groups and of the total series of 58, 53 per cent developed some form of unfavorable response. In no case, either in the group with rheumatic carditis or among patients with chorea, did the medication relieve the symptoms or hasten the recovery from the infection.

Vitamin C levels in the blood of 25 children with acute rheumatic fever were slightly lower than the average figures for 125 normal children examined by A. D. Kaiser.¹⁶⁴ Children with other types of acute infections frequently had smaller amounts of the vitamin than the average amounts of normal patients. Patients who were convalescent from rheumatic infections tended to have normal amounts of vitamin C and there has been no evidence produced that the administration of cevitic acid will prevent rheumatic disease or hasten its cure but apparently such a patient needs the vitamin and its administration is generally recommended in cases of rheumatic infection.

Larger amounts of vitamin C are excreted in the urine of children with rheumatic fever than in normal groups of the same age, according to the investigations of J. D. Keith and E. M. Hickmans.¹⁶⁵ Children receiving diets containing about 40 mg. of ascorbic acid, excreted vitamin C in various amounts with an average daily figure of 97 mg. Older children excreted more than younger ones, but wide variations were noted. Children with active rheumatic fever excreted more than the average amount of vitamin C and during convalescence their output returned to normal figures. The excretion could be increased by the administration of sodium salicylate, sodium bicarbonate and by induction of fever with injections of typhoid fever vaccine. There was some evidence that the stores of vitamin C were lower than average in rheumatic fever patients but no conclusion could be drawn that the infection was a result of this vitamin deficiency.

Diets of high nutritional value have been advised for children with rheumatic heart disease by S. E. Sadow, J. P. Hubbard and T. D. Jones.¹⁶⁶ One group

of 17 rheumatic children were given normal hospital diets and the other group of similar size received special food which had a 37.5 per cent higher caloric value and added vitamin content. Over a 6-month period of observation the experimental group made a greater weight gain than the control series. No other beneficial action on the course of the rheumatic infection was noted, but weight gain in itself has usually been considered as a favorable sign in the course of rheumatic fever.

A statistical survey of the influence of tonsillectomies on rheumatic infection has been made by R. Ash.¹⁶⁷ Of a total number of 521 patients under observation, 96 had had their tonsils removed before the time of the initial rheumatic infection and 425 had not been operated upon. When the 2 groups were compared in respect to the course of the infection, the mortality rates, and the reactions of the patients whose tonsils were removed in later years, no beneficial results from tonsillectomy could be discovered, especially when the natural differences of age, sex and race between the 2 groups were taken into consideration. The early removal of tonsils did not seem to delay the time of the initial infection nor did later tonsillectomy prevent recurrences of rheumatic manifestations and the development of cardiac disease. When the tonsils were removed shortly after the initial attack of rheumatic fever while the disease was still in its active state, the number of exacerbations was greater than when the tonsils were removed in a later period. The author concluded that the only indication for the removal of tonsils in rheumatic patients was a history of frequent infections at that site and then the operation should be performed at a time when there is no evidence of activity of the rheumatic infection.

INFANT FEEDING

By WALDO E. NELSON, M.D.

Breast Milk—R. M. Tyson, E. A. Shrader and H. H. Perlman¹⁶⁸ have attempted to determine whether certain of the laxative drugs may be transmitted through breast milk to the infant with any resulting effect upon it. By chemical analysis they could find no trace of phenolphthalein, calomel, senna, or rhubarb in breast milk after administration to the mother. In some instances, however, a laxative effect was noted in the infant after the administration of phenolphthalein, calomel or senna to the mother. On the other hand, both aloin and cascara were detected in the breast milk in a significant number of instances. In 87.5 per cent of the infants who received the milk with the positive aloin test, there was no evidence of any laxative effect. Cascara, however, showed both chemical and clinical evidence of transmission. In the case of rhubarb, there was no chemical or clinical evidence whatever of transmission.

Fat—Clinical experience in the feeding of newborn and premature infants with a formula in which virgin olive oil was substituted for butter fat, has been reported by M. L. Blatt and F. H. Harris.¹⁶⁹ This study was based on the work of Holt and his coworkers, in which they demonstrated that the unsaturated long chain, fatty acids, such as those found in olive oil, were better absorbed than the more saturated acids of cow's milk fat. The food employed in this study was a powder marketed under the name of "Olac" by Mead Johnson and Company. Its composition is approximately as follows: Skimmed milk 40.6 per cent; virgin olive oil 17.5 per cent, dextrimaltose 31.7 per cent, calcium caseinate 10.0 per cent, mineral ash 3.0 per cent and halibut liver oil 0.1

per cent. It has a caloric value of 134 per ounce ($3\frac{1}{2}$ level tablespoons). In preparation for feeding, 1 ounce of powder was added to 4 ounces of water, or 1 ounce added to 6 ounces of water. The more concentrated preparation has a caloric value of 27 per fluid ounce and the less concentrated of 19 calories per fluid ounce. The more concentrated preparation has the following approximate composition: Protein 4.7 per cent; fat 3.7 per cent, carbohydrate 10.7 per cent, and mineral ash 0.7 per cent; and the 19 calorie product approximately, protein 3.3 per cent, fat 2.6 per cent, carbohydrate 7.6 per cent, and mineral ash 0.5 per cent. The growth and development of the infants fed "Olac" compared favorably with that of similar infants fed human or evaporated milk. The authors conclude that Olac has proved satisfactory as an initial food for premature infants and is recommended as a complementary feeding for both normal and premature infants.

Sugar The rates of absorption of the various sugars used in infant feeding have been measured by F. W. Schlutz, E. M. Knott, J. L. Gedgoud and I. Loewenstamm.¹⁷⁰ The infants had a greater tolerance for glucose than did the children, while levulose gave somewhat similar results for the 2 age groups. The highest blood sugar curves were obtained with glucose, dextrimaltose, and Karo, while honey, sucrose, levulose, and lactose were next in order. Honey appeared to have special advantages for infants, because, with the exception of dextrose, it was absorbed most quickly during the first 15 minutes following ingestion, yet it did not flood the blood stream with exogenous sugar. It also maintained both a steady and slow de-

crease in blood sugar until the fasting level was again reached. The authors suggest that because of its widespread availability, palatability, and digestibility, it should have wider use in infant feeding.

Pasteurization—According to J. C. Geiger and C. Davis¹⁷¹ the phosphatase test of Kay and Graham is efficient for the determination of the adequacy of pasteurization of milk. For the benefit of those physicians who may be interested in this practical public health aspect, the technic of the phosphatase test of Kay and Graham is detailed below. The test as described by Geiger and Davis is as follows:

1 To 10 cc of a buffer substrate solution (1 tablet containing disodium phenolphosphate and sodium barbitone is dissolved in 50 cc of

water) contained in a 25 cc. stoppered test tube, add 0.5 cc of the milk and mix thoroughly.

2. Add two drops of chloroform, stopper the tube and incubate at from 98.6° to 100.4° F. (37° to 38° C.) for 1 hour.

3. At the end of this time, add 4.5 cc. of the diluted Folin and Ciocalteu reagent (1 volume of reagent to 2 volumes of water) mix, allow to stand for 3 minutes and filter.

4. To 10 cc. of the filtrate, add 2 cc. of the sodium carbonate solution (14 per cent anhydrous sodium carbonate), mix thoroughly and place in boiling water for 5 minutes and again filter.

5. Compare the color of the filtrate in a 13 mm. tube with the Lovibond standard 2.3 blue glass in the "Limitester."

If the color of the filtrate exceeds that of the standard glass, it may be safely assumed that the milk has been improperly pasteurized; that is, the temperature has been too low or the time of heating too short

JUVENILE DELINQUENCY

By ROBERT A. LYON, M D

In a review of 1660 cases referred to the California Bureau of Juvenile Research between the years of 1929 and 1934, N. Fenton and R. Wallace¹⁷² found that personality and behavior problems were more frequent abnormalities than delinquency. The relative frequency of the various types of patient are listed in the following tables

Etiology—The influence of *home environment* on elementary school children who have had behavior difficulties has been investigated by M. C. Hardy¹⁷³. Information for the study was obtained from school teachers, parents and pupils. A series of 144 poorly adjusted children were compared with 110 well-adjusted ones and, in summarizing the results, the author observed that in the homes of the maladjusted patients it was common to find the parents in poor health or that the parental relationships had

THE CLASSIFICATION OF CHILDREN'S PROBLEMS AND THEIR RELATIVE FREQUENCY IN THE CLINIC SERVICE OF THE CALIFORNIA BUREAU OF JUVENILE RESEARCH

Rank	Frequency	Per Cent
1. Personality Problems	380	22.89
2. Behavior Problems . . .	267	16.08
3. Delinquency	242	14.59
4. Predelinquency	212	12.77
5. Mental deficiency	200	12.41
6. Difficulties with School Subjects	178	10.72
7. Miscellaneous Problems .	122	7.35
8. Mental Diseases	53	3.19
Total	1660	100.00

(1 Juvenile Research 21: 144 (July) 1937)

been broken by divorce or separation, and employment of the mother outside of the home. In these homes the average age of the mother was lower than normal, and wide disparities of age often ex-

TABLE I

INCIDENCE OF SYMPTOMS AND PROBLEMS AMONG 795 CASES ARRANGED IN ORDER OF RANK

Rank	Symptoms and Problems	(N = 610) Boys		(N = 185) Girls		(N = 795) Total	
		Fre- quency	Rate per Case	Fre- quency	Rate per Case	Fre- quency	Rate per Case
1	Inadequate family relationships . . .	1408	2 31	476	2.57	1884	2 37
2	Problems of discipline and aggressive- ness . . .	917	1 50	232	1 26	1149	1.45
3	Educational maladjustment (other than discipline)	885	1 45	257	1 39	1142	1 44
4	Problems of immaturity	784	1 28	245	2 31	1029	1 29
5	Disturbances of emotional develop- ment and mood . . .	577	0 95	189	1 02	756	0 97
6	Antisocial behavior . . .	584	0 96	127	0 69	711	0 89
7	Problems of social adjustment . . .	386	0 63	111	0 60	497	0.63
8	Faulty parental attitudes toward child	296	0 49	111	0.60	497	0 63
9	Nervous disturbances and sleep dis- orders	294	0 48	105	0 57	399	0.50
10	Defects of physical well-being, appear- ance, and activity	280	0 37	78	0 42	303	0 38
11	Withdrawal tendencies	225	0 37	78	0 42	303	0 38
12	Economic problems . . .	184	0 30	55	0 30	239	0 30
13	Problems related to sex . . .	168	0 28	73	0 39	241	0 30
14	Speech problems	119	0 20	49	0 26	168	0 21
15	Problems of hereditary mental disease	87	0 14	29	0 16	116	0 15
16	Symptoms of neurosis or psychosis	8	0 01	10	0 06	18	0 02
		7202	11 81	2251	12 17	9453	11 89

(J. Juvenile Research 21: 177 (July) 1937)

isted between father and mother, and finally that the number of siblings was greater than average. Very often several of these factors occurred in combinations and it was concluded that they might have considerable influence upon abnormal behavior of the child in question.

Psychological factors contributing to the delinquency of girls has been studied by A. F. Jameson.¹⁷⁴ By means of intimate interviews and conferences with girls in an institution and by living with the patients so that she became interested in their problems, the author believed that she was able to gain a clearer insight into the background of the delinquency. The mental ages of the group were below average levels and their school achievement was slightly below their mental ability. About one-half of the girls came from broken homes and from families of low economic levels and a third of the

group had venereal disease. Many of the patients had followed a pattern of behavior consisting of early sex stimulation before the period of adolescence with a lack of parental supervision or any provision for normal activities and interests. Early in life the girls had become associated with persons whose chief interest was sexual indulgence and they had gradually adopted these practices themselves to the exclusion of other more normal social activities. It seemed that a great part of the behavior difficulty had arisen from the natural expression of a bodily function which had been directed into improper channels by poor environmental conditions.

The *causes of transiency* of 3352 boys between the ages of 16 and 20 years have been outlined by G. E. Outland.¹⁷⁵ The great majority of these boys had come from homes which were broken

by the death or absence of one or both parents. Many were members of large families which were unable to support the boys beyond the school years. Frequently trouble had arisen between various members of the family so that the boy had decided to leave his home. The general migration of young persons has been great during the past few years and it was believed that the social and environment conditions of the home were greatly responsible for the situation.

Intelligence Levels—The intelligence and achievement abilities of children in a delinquency area of Chicago which was characterized by low economic levels and a high degree of dependency, were examined by M. Lichtenstein and A. W. Brown.¹⁷⁶ Tests were made of the children in the fourth to eighth grades of 4 public schools and the general average of intelligence was lower (mean I Q = 91.7) than in the general population but was approximately the same as that of children from areas where there were high percentages of negro and foreign born inhabitants. Feeble-mindedness occurred in about 10 per cent of the entire group. Girls were generally younger and more intelligent than the boys in these grades, and there was a tendency for the average intelligence quotients of both sexes to fall with advancing age. All the pupils of the lower grades were retarded in the achievement tests although the results corresponded fairly well with their mental ages. Brighter children did less well in their achievement tests than their mental ages seemed to indicate. White children of both sexes tended to have higher levels of intelligence and achievement ability than the negro children.

The intelligence and physical status of 50 boys who were truant was compared with that of 50 delinquent boys who had never been truant, by W. C.

Murphy.¹⁷⁷ The average intelligence of the truant group was somewhat below that of the nontruant group and although superior types occurred in both groups of children, there were more of the mentally deficient in the truant series. In respect to educational achievement, the truant group was somewhat behind the other delinquent children, especially in subjects of language use, geography, physiology and hygiene. Defective vision and hearing were noted more frequently in the truant than the nontruant group but the height and weight levels of the 2 series were about the same. It was concluded that the special care of the truant child in respect to adapting his activities to manual rather than academic studies and the correction of his physical defects might lead to some reduction in the amount of truancy.

The *incidence* of mental retardation and the *characteristics of the mental defective* in a large group of juvenile delinquents has been reviewed by H. S. MacPherson.¹⁷⁸ Among 1000 delinquents observed in the Hartford Juvenile Court, approximately 20 per cent had intelligence quotients of 70 or below. The offenses of this group were usually severe and were about equally divided between thefts and a classification of "incurable" traits such as unmanageable behavior, running away, truancy and sex offenses. The great majority of such patients had been placed on probation, others had been reprimanded and a small group of 22 had been placed in institutions. Recidivism occurred in less than half of the group of mentally retarded delinquents and much more frequently in the boys than in the girls. The retarded children belonged to 1 of 2 general classes of conduct. The 1 group included children who were sensitive, docile, lazy, easily led, and the second

group was composed of individuals who were deceitful, quarrelsome, vulgar, destructive and unstable. This juvenile court had concluded that the mental defective could derive benefit from an institutional life which would supply the supervision and training not made available to the patients at their homes. These children should not be sent to correctional institutions but an emphasis should be placed upon the early recognition of the situation and the provision of special training and supervision. Finally, an adequate parole system should be maintained until the patient had become adjusted to community life.

A summary of 43 reports on the *intelligence quotients* of institutionalized juvenile delinquents has been prepared by M. B. Owen.¹⁷⁹ Of a total of 14,624 patients the average I. Q. was 82.5. The distribution is as follows:

I. Q. Group	Frequency
120 - up	124
110 - 120	759
90 - 110	4,025
80 - 90	3,655
70 - 80	3,488
Below 70	2,855
Total	14,624
Median	82.468
Q ₁	72.210
Q ₃	92.409
Q	10.088

(M. B. Owen: J. Juvenile Research 21: 199 (Oct.) 1937.)

Treatment—The methods and suggestions for the treatment of 795 juvenile delinquents have been formulated in Table II by N. Fenton.¹⁸⁰

The fundamental equipment necessary for the care of the mental health of children has been summarized by N. Fenton.¹⁸¹ He recommended that a child guidance clinic be established in the juvenile court and in all large school systems. There is a need for "hospital

schools" adequately staffed for the study and care of behavior problems, such an institution to replace the existing custodial types of correctional schools. Child guidance conferences in mental hygiene which should be held in every school, would bring the teachers into a closer relationship and a better understanding of the problems of their pupils. The foster home either in full-time or part-time capacity should be utilized as a place for the guidance of a child rather than for custody only. Finally, the need of parental instruction is great, especially when the parents themselves are disturbed by the behavior of the child. In the past, much emphasis has been placed upon material, equipment and buildings and an insufficient amount on the organization and provision of properly trained personnel to deal with the problems of juvenile delinquency.

The treatment of juvenile delinquency falls into categories of *punishment for the crime*, of *reward for good behavior*, or the *substitution of a poor environment with a good one* which permits the greatest possible development of an individual towards a satisfactory life. D. Carroll¹⁸² made a preliminary report of the camps which have been instituted to allow for self-government and self-instruction of the members. In the beginning, the patients aided in the development and building of the camp itself. To secure the best results from this type of free, unrestricted treatment, it has seemed the best to make a careful selection of the type of adolescent who is to attend. The group has included boys from 16 to 25 years of age, and the individuals who have profited most from this training have been the ones who had come from unsatisfactory environments with unsuitable homes and bad companions. It is the belief of the directors of the camp that these factors

TABLE II
FREQUENCY OF TYPES OF RECOMMENDATIONS MADE IN 795 CASES
(Arranged in Order of Rank)

Rank	Recommendation	Boys (N=610)		Girls (N=185)		Total (N=795)	
		Fre- quency	Rate per Case	Fre- quency	Rate per Case	Fre- quency	Rate per Case
1	Adjustment of home situation	2057	3.37	635	3.43	2692	3.38
	(a) Social or educational work in home	912	1.50	262	1.41	1174	1.48
	(b) Advice regarding methods of training	815	1.33	242	1.30	1057	1.32
	(c) Considerations of placement	229	0.38	88	0.48	317	0.40
	(d) Suggestions regarding sibling relationships	95	0.15	40	0.22	135	0.17
	(e) Interests	6	0.01	3	0.02	9	0.01
2	Educational adjustment	1608	2.64	490	2.65	2098	2.64
	(a) Modification of curriculum and instruction	844	1.38	243	1.31	1087	1.37
	(b) Classroom management	420	0.69	112	0.61	532	0.67
	(c) Placement and progress	235	0.39	77	0.42	312	0.39
	(d) Special individual guidance	109	0.18	58	0.31	167	0.21
3	Concerning physical well-being	866	1.42	292	1.58	1158	1.46
	(a) Specific treatments	431	0.70	133	0.72	564	0.71
	(b) Supplementary examinations	296	0.49	123	0.67	419	0.53
	(c) Operative therapy	139	0.23	36	0.19	175	0.22
4	Social adjustment in home, school, and community	642	1.05	167	0.90	809	1.02
	(a) Opportunities for adequate social relationships	318	0.52	94	0.51	412	0.52
	(b) Development of recreational and other special interests	164	0.27	51	0.27	215	0.27
	(c) Opportunity for employment	85	0.14	11	0.06	96	0.12
	(d) Special summer program	63	0.10	10	0.05	73	0.09
	(e) Enlistment of community aid	12	0.02	1	0.01	13	0.02
5	Miscellaneous	128	0.21	35	0.19	163	0.21
	Total	5301	8.69	1619	8.75	6920	8.71

(J. Juvenile Research 21: 227 (Oct.) 1937.)

TABLE III
TYPE OF PROBLEM IN RELATION TO ADJUSTMENT STATUS AS REPORTED IN FOLLOW-UP (JUNE, 1934)

	No of Cases	Per Cent Adjusted	Per Cent Partially Adjusted	Per Cent Improved	Per Cent Worst
Delinquency	125	32	44	19	5
Predelinquency	121	25	52	19	4
Behavior Problem	161	19	64	14	3
Personality Problem	190	26	55	17	2
Difficulty with School Subjects	74	15	61	20	4
Mental Deficiency	89	20	41	32	7
Mental Disease	33	18	49	27	6
Miscellaneous Problems	28	43	39	14	4
Total	821	24	53	19	4

(J. Juvenile Research 22: 52, (Jan.) 1938.)

of environment constitute a cause of delinquency which is more important than that of heredity or disease

Young adults with psychopathic tendencies have been eliminated from the camps because they seem to restrict the development and activity of the more normal members. One of the most characteristic features of the adolescents under observation has been the desire for attachment to someone and the individuals with inferiority types of personality have seemed to profit most from the camp life. As the result of careful physical and psychiatric examinations of the patients, many of those with slight aberrations of personality and those who have suffered from a lack of adequate training in previous years, have been benefited by the therapy although the camps have not been established for a sufficient length of time to allow for the fullest interpretation of the results.

A follow-up study of 821 patients who had been examined and treated by California child guidance units has been conducted by N. Fenton¹⁸³ Reports of success of treatment were sought from school teachers, parents and the members of the clinic staffs. General agreement of reports from these sources was obtained in approximately 72 per cent of cases. The results have been recorded in Table III.

Sources of error in the interpretation of such figures include overenthusiasm in interpretation of the outcome, especially in relationship to the importance of clinic treatment. It was suggested that several other factors may have led to changes in the child's behavior such as growth and maturity, the influence of friends and teachers. Difficulties in setting up clear-cut objective measurements of adjustment also make such interpretations difficult.

MEASLES

By ROBERT A. LYON, M.D.

Among the *unusual forms of measles rashes* are large bullous lesions which have been described recently by G. W. Ronaldson¹⁸⁴ In 1 patient, 4 years of age and in another, 10 months old, the lesions resembled pemphigus in many respects. The older child recovered completely although raw denuded areas were left by the desquamation of the skin over the large bullae. The other patient died as a result of a complicating bronchopneumonia. In a review of the literature the author found that 3 general types of lesions of this type had been described. A bullous eruption may be associated with measles but not necessarily due to the measles rash itself. In the second type of cases such as were described

above, the bullous eruption occurred as a part of the measles exanthem and, finally, a true pemphigus may develop after the appearance of a measles rash.

Complications—A patient who developed *gangrene* of 1 leg following an attack of measles has been described by S. Bartsocas and Grignon¹⁸⁵ The child, 2 years of age, who had developed a typical measles rash, complained of pain in the right leg which soon grew cold and pale and later became edematous and blue. The foot finally turned black and an ulceration developed on the upper surface. Within a few days the child died in a convulsive attack. The lesion seemed to be vascular in origin because there had been no other abrasions or

infections of the leg at the time of the onset of the disease.

In a report of 2 patients who died from postmeasles *encephalitis*, N. Malamud¹⁸⁶ reviewed the general pathologic characteristics of the disease. The infection in the brain seemed to follow 3 routes of distribution: (a) The earliest changes occurred in the perivascular areas spreading from the white to the gray matter; (b) a subependymal distribution was noted in the periventricular tissues and basal ganglia, and (c) marginal involvement occurred in the brain stem. Congestion, hemorrhage, demyelination and glial proliferation were also noted. The spread of the infection and the degree of involvement vary with the severity of the disease. Inflammatory changes alone resulted from infections of short duration while degenerative signs and depositions with glial tissue were noted in patients with prolonged infections. Considerable difference existed between the lesions of post-measles encephalitis and multiple sclerosis when the various stages of the 2 infections were studied, and it was concluded that, from a pathological viewpoint, the encephalitis of measles was a true infectious process probably caused by the virus of that disease.

Three instances of *acute appendicitis* arising during the course of measles have been observed by E. Angel and A. Kizinski.¹⁸⁷ The ages of these patients varied from 15 to 22 years and complete recovery occurred in every case. In reviewing a group of 35 reports of this condition which have appeared in the medical literature, the authors found that the chief diagnostic points were the typical abdominal pain on the right side accompanied by vomiting. These symptoms may develop before, during or after the appearance of the rash and the white count may be below or above the levels

of normal patients so that the diagnosis must rest entirely upon clinical findings. Operation seemed to be indicated in all instances when the acute attack of measles did not greatly increase the risk, and in such cases constant observation of the patient was necessary.

The pathological changes occurring in 100 cases of measles have been reviewed by J. A. Degen, Jr.¹⁸⁸ The majority of his patients were children under 2 years of age and no specific lesion characteristic of the infection was observed in any of the organs of the body. The occurrence of pneumonia and toxic changes were frequent findings but the type of pneumonia varied in its characteristics. Secondary infections, frequently of the streptococcic variety, often produced an interstitial mononuclear cell infiltration of the lungs which resembled that found in the course of scarlet fever. The most frequent complications of the measles were pneumonia, laryngitis, and encephalitis. Death was most frequent in the second or third week of the disease. It was felt that many of the complications of measles were due to the streptococcus which seemed to be spread by means of the blood stream.

Diagnosis—The wide distribution of *inclusion bodies* in the various tissues and secretions of a measles patient has been emphasized by A. C. Coles.¹⁸⁹ He noted them in the blood, the secretions of the nose, throat and lachrymal glands, in scrapings of the skin and of Koplik spots, and even in the breath moisture caught upon a slide, or in the cold water washings of a handkerchief. In control studies, no such inclusion bodies were noted except in patients with early stages of a cold, or some of the skin diseases such as psoriasis, herpes and lichen planus.

Inclusion bodies and cellular disintegration in the scrapings from nasal mucous

membrane and from Koplik spots of the buccal cavity of measles patients have been described by J. Broadhurst, M. E. MacLean and V. Saurino.¹⁹⁰ Dry or slightly moistened swabs were employed in securing the smears of 110 patients examined on the second to fourteenth day of the disease. The number of cells affected by the disease seemed to increase as the disease progressed and were present for at least 12 days after the onset of symptoms. Koplik spots contained such cells in all but 3 of a series of 14 patients on the third to the sixth day of the disease. Nigrosin in a 1 per cent aqueous solution was employed as the staining material. The inclusion bodies of measles were considerably different than those observed in other throat infections and the tissue cells seemed to be in a process of disintegration with the margin of the cell especially affected by a necrotic process. Inclusion bodies were not found in normal persons nor in those with diseases other than measles or other virus infections.

Inclusion bodies have been noted in the blood of measles patients from the day before the appearance of rash until the tenth day after the onset of the eruption by J. Broadhurst, G. Cameron and V. Saurino.¹⁹¹ Their staining technique employed methylene blue as the dye. The inclusion bodies, varying in size from pinpoint to large globules, sometimes assuming crescent shapes, were easily visible in mononuclear cells. These cells appeared to be in various stages of disintegration with a pale nucleus, heavy granular cytoplasm and irregular borders exhibiting protrusions and indentations. Tissue cultures prepared from the white cell layers of centrifuged blood of measles patients on the third to seventh day of the disease exhibited characteristics much the same as described above, except that

giant cells were encountered and the "explosive destruction" of the white cells was more marked.

Treatment and Prevention—In an attempt to reduce the incidence of complications of measles, **vaccines** containing equal amounts of pneumococci, hemolytic streptococci and Pfeiffer's bacilli have been employed by A. A. Cunningham.¹⁹² The adult dosage was considered to be 200 million killed organisms of each kind and this was reduced for children so that a child of 1 year received about 20 million of each. Three subcutaneous injections at intervals of 24 hours were administered to 236 patients, mostly under 5 years of age, who were in the early stages of the disease. In no case was the vaccine given to a patient with a fading rash. In a comparison of the incidence of complications in this group with that of an untreated control group of approximately the same size, no advantages could be noted as a result of the inoculations. Pulmonary and ear complications were approximately the same in the 2 groups.

In a review of the methods of prevention and modification of measles, C. F. McKhann¹⁹³ called attention to the general decrease in incidence and mortality of that disease during the past few years. This reduction may have been due, in part, to the public's recognition of the danger of the disease, and the better care and isolation which was being instituted. Other factors which have had an influence were the general improvement of the health of children, which is reflected in the reduction in the number of nutritional disorders and deficiency diseases, and the current tendency to care for measles in the home, thereby avoiding exposure to other infections in the hospital. There also is a possibility that the incidence and virulence

TABLE IV

COMPARISON OF THE EFFICACY OF ADULT SERUM, CONVALESCENT SERUM AND PLACENTAL EXTRACT IN THE PREVENTION AND MODIFICATION OF MEASLES (ALL TYPES OF EXPOSURES), BASED ON FIGURES COLLECTED FROM THE LITERATURE

Source of Immune Bodies	Number of Cases	Protected		Modified		Failed	
		Number	Per Cent	Number	Per Cent	Number	Per Cent
Adult Serum	584	329	56.4	139	23.8	116	19.8
Convalescent Serum	1627	1227	75.4	273	16.8	127	7.8
Placental Extract	2740	1762	64.3	833	30.4	145	5.3

TABLE V

PLACENTAL EXTRACT IN THE PREVENTION OR MODIFICATION OF MEASLES (INTIMATE EXPOSURES)

	Given to Protect				Given to Modify			
	Cases	Protected	Modified	Failed	Cases	Protected	Modified	Failed
Laboratory Extract	556	302	222	32	1159	512	556	91
Commercial Extract	29	13	13	3	104	70	30	4
Total . . .	585	315	235	35	1263	582	586	95
Percentage . .		53.8	40.4	5.8		46.1	46.4	7.5
		94.2				92.5		

of the disease may tend to vary in periodic sequences.

The methods of producing active immunity to measles have not proved successful and the only way to decrease the morbidity and mortality has been passive immunization with *human immune bodies*. Human convalescent serum has proved the most effective material for the protection against measles and, in the absence of that, human adult immune serum or whole blood has been employed as a substitute. The recent development of the immune globulin extracted from placental tissue has provided an inexpensive and available material of the same type. The author has compared the results of adult serum, convalescent serum and placental extract in the modification of measles. In groups of patients varying from more than 500 to 2700, the placental extract protected the patient from measles or modified the

attack in all but 5 per cent of cases; the convalescent serum failed in about 8 per cent and adult serum in approximately 20 per cent of cases. These results would indicate that adult serum is the least practical for this purpose although it is possible that, with doses of increased size or potency, the serum might have been more effective.

The dosage of *placental extract* and its potency are determined by the experimental testing of each lot. The total nitrogen content has been an indication of potency but the method of estimation of its strength from the diphtheria antitoxin content of the extract has not proved satisfactory. When the placental extract was given in adequate dosage during the first 4 days after exposure to the disease, modification or protection occurred in 94 per cent of cases. When given on the sixth, or preferably the eighth day, after exposure, the extract

TABLE VI
PLACENTAL EXTRACT, REACTIONS TO INTRAMUSCULAR INJECTION

Total Number of Cases	No Reactions		Local Reactions				Febrile Reactions			
			Mild		Moderately Severe		Mild		101 F. or Over	
	Num- ber	Per Cent	Num- ber	Per Cent	Num- ber	Per Cent	Num- ber	Per Cent	Num- ber	Per Cent
2896	1659	57.2	1058	36.7	142	4.9	578	19.9	86	2.9

(C. F. McKhann, J. A. M. A. 109:2034, (Dec. 18) 1937.)

caused modification or protection in 93 per cent of a series of 585 cases (see Tables IV and V).

The reactions of the patients varied in intensity. Following the intramuscular injection of the material in a series of 2896 patients, no reactions developed in 57 per cent, mild local reactions occurred in 37 per cent, moderately severe reactions limited to the site of injection in 5 per cent. Systemic reactions consisting of a slight rise in temperature were noted in 20 per cent and a severe febrile response in 3 per cent. Allergic manifestations were observed in 3 patients 2 of whom had a history of an allergic response to other materials (see Table VI). The author concluded that the placental extract was a readily available material capable of providing passive immunity of short duration. It may be used effectively in giving complete protection from measles by administering it in adequate dosage during the first 4 days after exposure to infants who are suffering from chronic illness or some nutritional disturbance and it may be employed as a means of attenuating the disease in normal healthy children by giving it 5 to 9 days after the patient's exposure to the infection.

The value of *convalescent serum* in the protection and modification of measles has been emphasized in the report of C. M. Hyland and L. R. Anderson.¹⁹⁴

In a series of 423 patients inoculated with human convalescent serum, approximately 73 per cent were completely protected against the disease and 25 per cent had modified attacks which made a total of 98 per cent who were distinctly benefited by the injection of serum. In older patients, complete protection from the disease could be obtained in higher percentages when larger doses of serum were administered. In the younger age groups the standard dosage provided complete protection in almost all instances. The optimum dosage for different age groups has been difficult to determine because of the variation in the potency of the serum employed. Until better methods of standardization of the serum are available, the authors concluded that the ordinary dosage should be 2½ to 4 cc. for children under 3 years of age and 5 to 8 cc. for older patients. When modified attacks of measles are desired instead of complete protection, the dosage may be lowered or the serum injection must be delayed until after the fourth or fifth day of the incubation period. Serum administered as late as the thirteenth or fourteenth day of the incubation period seemed to modify the disease. In 7 instances in which the serum had been injected just before the appearance of the rash, the disease was modified in 4 instances and not affected in 3.

TABLE VII

RESULTS OF PROTECTION EXPERIMENTS WITH CONVALESCENT SERUM, ADULT SERUM, AND PLACENTAL EXTRACTS AMONGST CHILDREN 0-10 YEARS DURING THE EPIDEMIC PERIOD 1935-36

Serum	Number of Children Observed	Results %		
		Protected	Attenuated	Unmodified
Convalescent	109	71.6	25.7	2.7
Adult	1033	72.1	17.3	10.6
(Pseudoglobulin)	9	100.0		
(Euglobulin)	13	61.5	23.1	15.4
P. E. (Lister)	20	60.0	25.0	15.0
(L. C. C. euglobulin)	12	75.0	16.7	8.3
(L. C. C. pseudoglobulin)	4		50.0	50.0
(Lederle)	14		50.0	50.0
(Type unknown)	40			
		77.3	13.6	9.1
		67.8	17.8	14.4

(W. Gunn, Proc. Roy. Soc. Med. 31: 835 (May) 1938.)

TABLE VIII

COMPARISON OF CONVALESCENT AND ADULT SERUMS ACCORDING TO AGE PERIODS, IN 1935-36 EPIDEMIC (AIM = PROTECTION)

Age Group	Convalescent Serum		Adult Serum	
	Observed	% Protected	Observed	% Protected
0-6 months	2	100.0	123	92.7
6-12 months	19	78.9	150	74.7
1-3 years	50	70.0	456	63.6
3-5 years	27	63.0	194	73.7
5-10 years	11	81.8	110	78.2
10+ years	3	100.0	22	86.4
All ages	112	72.3	1055	72.4

(W. Gunn, Proc. Roy. Soc. Med. 31: 835 (May) 1938.)

Convalescent serum or immune adult serum have proven more satisfactory in the prevention or attenuation of measles than placental extracts in the experience of M. L. Bridgeman¹⁹⁵. The placental extracts seemed to give more severe local reactions and the failures in producing the desired results were more numerous. In a series of 228 children treated by all methods, 15 cases of unmodified measles developed (6.6 per cent). Among 177 patients treated with convalescent serum or immune adult serum, only 1.7 per cent had unmodified attacks. The adult serum was given in doses of 6 to 12 cc. on the fourth to seventh day of the incubation period to

modify the disease. Later than this, larger doses were required to affect the course of the illness.

Good results in checking an epidemic of measles in a boys' school were obtained with the use of adult serum by K. LeFleming¹⁹⁶. When the disease broke out, serum was administered in doses of 10 cc. to 20 patients during their incubation periods, to 50 patients before their direct exposure to the disease and the serum was not given to a group of 15 including the patient with the original infection. The treated patients seemed to have milder symptoms and fewer complications than the control group. No reactions occurred as the result of the

TABLE IX

COMPARISON OF (a) CONTROLS (UNINJECTED), (b) ATTENUATED, AND (c) UNMODIFIED
ATTACKS, AFTER SERUM ADMINISTRATION
London County Council—Measles

	Observed	With Complications	Deaths
Attenuated Cases	273	25 (9.2%)	1 (0.4%)
Unmodified Cases	144	55 (38.2%)	9 (6.3%)
Primary Infecting Cases	84	28 (33.3%)	3 (3.6%)
Controls Other Than Primary	329	52 (15.8%)	10 (3.0%)

TABLE X

AGE DISTRIBUTION OF ABOVE CASES

Age Group	Primary Cases (Controls)	Attenuated Attacks	Unmodified Attacks
0- $\frac{1}{2}$ year.		7 (2.6%)	3 (2.1%)
$\frac{1}{2}$ -1 year	5 (6.2%)	24 (8.8%)	23 (16.0%)
1-3 years	41 (50.6%)	133 (48.7%)	88 (61.1%)
3-5 years	20 (24.7%)	79 (28.9%)	19 (13.2%)
5-10 years	14 (17.3%)	27 (9.9%)	9 (6.2%)
10+ years	1 (1.2%)	3 (1.1%)	2 (1.4%)
All ages.	81 (100.0%)	273 (100.0%)	144 (100.0%)

(W. Gunn, Proc. Roy. Soc. Med. 31: 837 (May) 1938.)

injections. The most advantageous time to administer the serum in the case of school epidemics was thought to be the first few days after the outbreak of the disease and the preventive program should include as large a proportion of the school population as possible.

An outbreak of measles in a children's hospital usually requires immediate steps to prevent the occurrence of any cross infections. To accomplish this, W. F. Crosbie¹⁹⁷ injected all susceptible patients on the third or fourth day of exposure with immune adult serum or placental extract. The former was administered to 124 children in doses of 15 cc. Placental extract was given to 84 patients in doses of 10 cc. and to groups of small number in 6 and 4 cc. doses. The smaller doses did not give adequate protection or modification of the disease, although no complications occurred. The adult serum and the

larger doses of placental extract prevented or modified the illness in the other patients and frequently prolonged the incubation period to 15 to 21 or more days. When the results were analyzed according to age groups of the children, it was noted that younger children seemed to require as large or larger doses of protective material than older age groups.

An evaluation of therapeutic measures to control measles has been made by W. Gunn¹⁹⁸ from a statistical analysis of the results obtained in several recent epidemics of the disease in London. Convalescent serum and adult serum seemed to be equally effective in producing the desired results and placental extracts were slightly less potent, as Table VII indicates.

When the age of the patient was taken into consideration the figures showed higher degrees of protection in age

groups under 6 months and over 10 years and it might be concluded that the dosage for patients of the 1- to 10-year age groups should be increased (Table VIII)

The desired results with injections were somewhat better when only attenuation of the infection was desired and the serum was administered after the sixth day of exposure. It was also learned that the serum administrations were equally effective in children who had been exposed to measles for long or short periods of time. The "quantity" of infection, therefore, seemed to play a less important rôle in producing massive infections than has been suggested by other investigators. Patients who obtained some benefit from the serum injections had fewer complications and much lower mortality rates than an untreated control series. Patients who did not receive benefit from the serum had more complications and higher death rates than untreated control groups, possibly because the former series of children were frequently suffering from other illnesses when they contracted the disease (Tables IX and X)

An interesting observation was the tendency for increasing efficiency of adult serum as epidemics were prolonged as if the progressive intimacy of the donors with the infection increased the titer of immune bodies in their serum as the epidemic continued

Globulin fractions prepared from *immune adult serum* have been effective in protecting children from measles in the experiments reported by S. Kare-litz¹⁹⁹ By concentrating the serum, the quantity injected could be greatly reduced and the effectiveness maintained. Given to children exposed to measles, this globulin extract protected them from the infection or modified the disease satisfactorily and the reactions were less than those obtained with globulin concentrates of placental extracts.

Local inhibition of the rash of measles may be produced by the intradermal injection of *human convalescent serum* into the skin. That this phenomenon might be employed as the *test of potency* of convalescent serum or immune adult serum was the opinion of W. R. Phillips.²⁰⁰ The injection of 1 cc. of convalescent serum prevented the development of the rash in 30 instances in a series of 50 measles patients when injections were made 36 hours or more before the appearance of the rash. Non-immune adult serum, horse serum and normal saline solutions did not produce this reaction. Convalescent serum diluted to as low as 2 to 5 per cent with normal saline protected the skin from the rash. By this method it was hoped to establish some criteria for judging the protective value of products such as immune adult serum and placental extracts

MENTAL DEFICIENCY IN CHILDREN

By ROBERT A. LYON, M.D.

The relationship between *intelligence levels* and the patients' *height* and *weight* has been surveyed by N. A. Dayton.²⁰¹ His material was obtained from the study of 31,939 pupils of the public schools of Massachusetts. The majority

of the children were 8 to 14 years of age and their mental status was determined by intelligence tests. About 16,000 were dull or borderline cases and 13,000 were mentally defective. The ranking of these pupils corresponded very

closely with their achievement in school, and the difficulties with school work experienced by the retarded group appeared very early in their school life. Only a few of the patients were distinctly pathological with psychotic or neurological disturbances. The children with normal intelligence who were tall and normal in weight had higher average intelligence levels than those who were short or overweight.

The same general tendency occurred in the retarded children. The retarded children and the mental defectives who were tall and average in weight had higher levels of intelligence than the children who were short and below or above average in weight. The author stressed the point that these figures concern children in the growing stage of life and are not applicable to adult life. The above figures provided statistical evidence that children with slow mental processes might also have some disturbance of growth and metabolism and it was suggested that a child's height and mineral metabolism might be linked with the development of his central nervous system and that the retarded mentality of children with abnormalities of weight might be related to the metabolism of fats, carbohydrates and proteins.

Characteristic *biochemical changes* associated with certain types of mental deficiency have been reviewed by G. A. Jervis²⁰² He mentioned the disturbances of protein metabolism resulting in the production of phenylpyruvic acid in specific types of low grade mental defectives, the increased lipid content of body tissues in patients with amaurotic familial idiocy and the metabolic disorders accompanying lesions of the basal ganglia in other types of mental defectives. The cause of such disturbances does not seem to have any relationship

to environment, the age of the parents, the order of birth or infectious diseases, but seems more likely to be the result of a genetic recessive mechanism. This latter conclusion is justified from a statistical analysis of the reported cases of these disturbances. Other conditions associated with biochemical alterations include albinism, muscular dystrophies and disturbances of glycogen metabolism and storage. The author concluded that some of the metabolic disturbances might be the result of the inheritance of biochemical characteristics, such as the absence of a specific enzyme, and further study of this problem from a genetic standpoint might be profitable.

A comparison of the incidence of *physical defects* in 900 mentally retarded children and in 2700 normal children has been made by M. Goldwasser.²⁰³ The most common physical defects noted in both groups were dental caries, diseased tonsils, poor nutrition, improper posture, and impaired vision and hearing. The incidence of these defects was slightly greater in the retarded children and there were fewer individuals of this group who were entirely free from defects.

Recent discussions of the problem of feeble-mindedness in Germany have been reported recently. Von Verschuer²⁰⁴ has estimated that there are approximately 400,000 feeble-minded persons in Germany, a percentage of 0.6 of the population, although this figure may not include many individuals in the dull, borderline mental levels. About 40,000 to 50,000 feeble-minded persons are being cared for in institutions and about 2 to 3 per cent of school children are in special schools. The great majority of feeble-minded persons (80 per cent) seem to owe their condition to hereditary factors, the remainder to environment.

In a series of 254 pupils in special schools, Lechner (*ibid*) has also reported an incidence of about 81 per cent who were congenitally affected. Low intelligence levels and alcoholism were conspicuous characteristics of their parents. Approximately two-thirds of the children are the result of sexual desires of parents who were mentally or neurologically unfit. In about a fourth of the group, 1 parent or grandparent had an addiction to alcohol which indicated his unfitness to have children. It was doubted whether sterilization or eugenic laws would eliminate this type of propagation.

The characteristics and background of mental defectives of the higher levels have been surveyed from the observation of a group of 1000 patients with intelligence quotients of 50 or above, by E. J. Humphreys, G. W. T. Watts and W. H. Boldt.²⁰⁵ More than 700 of this group were children less than 15 years of age. In the summary of the obstetric and pediatric factors which may have had an influence on the development of mental deficiency, the authors found that the health of about 20 per cent of the parents was impaired by venereal disease, tuberculosis, heart trouble or nervous and mental afflictions. The mental condition of the mother was unsatisfactory just before delivery of more than half of the patients. Birth was prolonged in 15 per cent of the series and instrumental deliveries occurred in 10 per cent. Their families tended to be larger than average and illegitimacy occurred in 20 per cent of the cases. Mental deficiency of the children was most apt to be noted during the first year of life by their inability to walk and talk and at the time of entering school. At this latter time 78 per cent of the group were suspected as being mentally deficient. A history of convulsions was elicited in 89 per cent of the group and an accident

in 11.7 per cent but otherwise the childhood diseases occurred no more frequently than in normal groups of children.

A study of the parents showed that about 28 per cent had no knowledge of their children's mental defects. Discipline maintained at home had been excessive in 27 per cent of instances and inadequate in about half of the cases. Inadequate supervision and care of the home, failure to provide a satisfactory standard of living, were frequently noted. The community complaints against the feeble-minded individuals indicated that there were 6 general types of patients exhibiting symptoms of depressed motor activity, instability, destructiveness, sexual hyperactivity, moodiness with depressions and fears and, finally, misdirected social activities including stealing and truancy. It was usually the restless type of behavior which led to institutionalization of the patient and programs for the care of such individuals are especially necessary. The authors suggested that the educational system of a community make more adequate provision for the care of the mental defective of higher levels rather than entrust such care to an institution for the feeble-minded.

The effects of *lethargic encephalitis* on intelligence have been investigated by A. W. Brown, R. L. Jenkins and L. E. Cisler.²⁰⁶ Their group consisted of 108 patients between the ages of 2 and 26 years with a mean age of 12.2 years. Mental growth was tested over a period of a few months to 13 years. The intelligence levels of the group were lower than average at the time of the first examination. The presence or absence of parkinsonian symptoms did not alter the rate of mental growth and the patients with behavior disorder deteriorated more rapidly than the other

children but the differences were not significant. Children who developed encephalitis before the age of 10 years had somewhat greater decreases of intelligence than the patients who contracted the illness later in life. The damage to the brain substance by the encephalitis did not seem to be the sole cause for intelligence changes and the presence of a more progressive type of brain lesion was suggested by the plotted curves of their mental development.

The *mental growth of epileptic children* has been observed recently by I. N. Kugelmass, L. E. Poull and J. Rudnick²⁰⁷ A series of 129 children with epilepsy were selected from institutions and private practice. The onset of epilepsy had occurred at various ages from birth to 15 years but the majority of patients had their first attacks in pre-school years. The treatment of the hospitalized children had consisted chiefly of *general hygienic measures* and the administration of *phenobarbital*, while that of most of the children living at home had included *ketogenic diets*. The mental levels of the institutional group were lower than those of the private practice series but retests made 3 months to 3 years later indicated that the mental growth of both groups was definitely correlated to the progress of the epilepsy. If the number and intensity of the convulsive attacks tended to diminish, the mentality grew while the children who did not show clinical improvement deteriorated mentally.

Mongolian Idiocy

In a survey of a large number of cases of Mongolism from the clinics of this country and Europe, A. Bleyer²⁰⁸ found that the age of the mother was the most important factor related to the incidence of this condition. In a series of 2800 case histories of Mongolian idiots, con-

sideration was given to such influences as advanced maternal age, advanced paternal age, the immaturity of either parent, great differences between the ages of the parents, the place of the Mongolian idiot in the relationship to the other members of the family and the possibility of reproductive exhaustion from a long series of pregnancies. There was inadequate evidence that any of the factors were definitely related to Mongolism except the advanced age of the mother. Mongolism occurred with considerable infrequency in the early child-bearing years but after the mother had reached the age of 30 years, the condition appeared more frequently in the offspring and after the maternal age of 40 the incidence of the defect in infants increased greatly, regardless of the number of previous pregnancies or the place of the child in the family.

Mongolian idiocy was originally thought to occur much more frequently in the white race than in any other, but in recent years the reports would indicate that the condition is more widely disseminated. A total of 36 cases of Mongolism have been observed in the negro race including 3 recently reported by R. B. Scott²⁰⁹ His patients were 9½ months, 9 years and 3½ years of age respectively when the diagnosis was made.

Hydrocephalus

An investigation of the mentality of 5 patients with hydrocephalic conditions which had been relieved by the coagulation of the choroid plexus was reported by T. J. Putnam²¹⁰ In 1 to 3 years after the operation, 3 children were found to be of approximate normal mentality for their ages, as judged by Kuhlman tests. The 2 other children appeared normal in mental development but 1 subsequently died of a broncho-

pneumonia and the other had not been observed for a sufficient length of time since operation to judge the progress of mental development. In a total series of 26 patients with hydrocephalus, death had occurred as the result of operation in 10 instances. The author did not recommend choroid plexus coagulation in patients with high degrees of mental deterioration.

The value of removing the choroid plexus in patients with internal hydrocephalus has been questioned by G. B. Hassin, E. Oldberg and M. Tinsley.²¹¹ In experiments with dogs, the removal of 1 choroid plexus gave various results, a decrease in ventricular size in some

cases, no change in dimensions in others, and sometimes an increase in size of the affected ventricle. Many structural changes occurred in the brain together with inflammatory reactions and scar tissue formation which may have affected the results. In patients with hydrocephalus, the removal of the choroid plexus did not always seem to cause a diminution of the amount of cerebrospinal fluid secreted. It was questionable whether the choroid plexus actually secretes the fluid or if so, whether it is the only mechanism for its production. The treatment of hydrocephalus by treatment of the choroid plexus seemed to be a procedure of very doubtful benefit.

MUMPS

By ROBERT A. LYON, M.D.

Etiology—Since mumps can be produced in monkeys by the injection of Stenson's duct with human saliva, it has been concluded that a virus is the etiologic factor. Further evidence of the specificity of this virus has been furnished by the work of O. Bloch, Jr.²¹² In 37 animals, the infection was produced by inoculation of Stenson's duct with infectious human saliva. Focal acinar necrosis, with edema of the gland and a febrile reaction, were consistent results. When other substances were injected into the duct, such as a boiled gland suspension from an infected patient, normal monkey parotid suspensions, granular mucin, soluble starch in a saline solution, fresh white of an egg or vaccinia virus, no typical reactions of mumps were obtained. One of the histologic changes, the development of inclusion bodies in the cellular cytoplasm of the glands which occurred frequently in mumps, could also be detected after the

injection of normal saliva so that this type of reaction seemed to be typical of virus infections but could not be said to be a specific result of a mumps infection.

Assuming that mumps is a generalized infection and may produce many types of systemic manifestations, J. A. Greene and R. H. Heeren²¹³ wondered whether the spleen might show evidence of involvement. In a series of 25 patients with mumps, the majority of whom were adults, the spleen was found to be palpable in 14 instances. In a control series of 25 unselected cases the spleen was found to be palpable in only 5. Usually the splenic enlargement occurred early in the disease and when the incidence of complications in a series of 100 patients was reviewed it was found that 30 per cent had some type of complication outside of the salivary gland enlargement and about 47 per cent of these patients developed a complication as 1 of the first manifestations of the disease. These find-

ings were considered to be additional evidence that the infection was a generalized one involving several or many organs of the body.

The injection of rabbits with the cerebrospinal fluid from patients with mumps caused changes in the brains of these animals. These experiments were conducted by V. de Lavergne, P. Kissel and H. Accoyer.²¹⁴ Most of the rabbits developed a lymphocytic response and, when this reaction persisted, anatomic changes occurred in the region of the neuraxones. Such pathologic responses were even produced by the patients' cerebrospinal fluids which contained no increase of cellular elements and by the fluids of patients who had no clinical evidence of nervous tissue involvement.

Complications — *Encephalitis* due to the virus of mumps without any evidence of salivary glandular enlargement has been observed in a child 4 years of age by P. F. Armand-Dehille, Wolmetz and Barbery.²¹⁵ The patient developed symptoms of fever, severe vomiting and headache, and more than 500 cells, mostly lymphocytes, were found in the cerebrospinal fluid. There was no evidence of tuberculosis, syphilis or infective bacteria in the fluid and only the history of mumps in other members of the family led to the final diagnosis. An older sister had developed typical mumps 19 days previously and the mother of the 2 children contracted the disease several hours after the encephalitic symptoms of the patient were noted. The course of the encephalitis was benign and complete recovery occurred within a week.

The occurrence of *orchitis* of mumps without any parotid swelling was noted in a patient of J. R. Hild.²¹⁶ The etiology of the testicular infection was suspected when it was found that a brother had had a typical attack of parotitis 17 days previously. A sister developed

mumps a week after the onset of her brother's orchitis.

An unusual complication of mumps, *transverse myelitis*, has been reported from 2 sources during the past year. One patient, a male 39 years of age, was observed by A. C. Fortney.²¹⁷ Twelve days after the onset of mumps, the patient stated that the soles of both feet began to tingle. Within the next few days his legs became paralyzed and he lost control of the bladder and rectal sphincters. Sensation of the skin was diminished from the level of the third rib downward and within a short time the left arm became paralyzed. During the next 5 months the patient made a slow but complete recovery. Only 3 other such cases have been reported in the medical literature with 1 death and only a very slow and minimal improvement in the other cases. Repeated spinal punctures and the employment of convalescent serum were suggested as the methods of treatment.

The other case of *myelitis* was noted by A. Lemierre and M. Morn.²¹⁸ The patient, 19 years of age, developed parotitis and orchitis. On the sixth day after the onset of the illness, he developed urinary retention, loss of the tendon reflexes of both legs and arms, a bilateral positive Babinski sign and a positive Oppenheim reflex on the right side. Recovery was complete.

Another unusual complication of mumps was observed by E. Gourion and H. Marçon.²¹⁹ Their patient developed a *phlebitis* of the left leg 20 days after the onset of mumps. He also had a bilateral orchitis, more marked on the left side. It seemed possible that the phlebitis occurred either as an unusual localization of the circulating virus, or as an infection spreading from the inflamed testes. Except for evidence of a small pulmonary embolus, convalescence was normal and recovery was complete.

NEWBORN

By ROBERT A. LYON, M.D.

In an extensive survey of the *incidence and causes of neonatal deaths*, B. E. Bonar²²⁰ called attention to the problems confronting the pediatrician and obstetrician. The mortality rates for infants under 1 year of age have declined about 40 per cent during the past 20 years. For infants less than a month of age the decline has been only 27 per cent, for those less than 1 week of age, 17 per cent, and for those under 1 day, only 4 per cent. Further reduction of the total infant mortality rates seems to be a problem of the obstetrician primarily. Certain factors such as the increasing age of the women bearing children, the lowered birth rate which increases the relative number of first born children, and the tendency to improve the health of certain women of impaired vitality may be factors which increase neonatal deaths. Other conditions over which the obstetrician has greater control are: (a) The improper use of anesthetics, analgesics and other drugs which may be injurious to mother and child or may prolong labor, and (b) unnecessary or improper operative procedures.

Of utmost importance in the reduction of neonatal mortality rates is more thorough study of the causes of death. It was suggested that the International List of Causes of Death be revised to eliminate ambiguous and misleading terms. Following the classification of Cruickshank, the author believed that most of the deaths could be grouped as those due to birth injuries, infections and gross congenital defects. Cases of sudden death and others of obscure nature require careful investigation of factors of age and maturity at the time of death, the mode of delivery, the examination of

the placenta, the ante mortem observations and finally the autopsy examination, together with all the laboratory and technical tests available. The author advocated an extension of research into the antenatal and natal problems of physiology and pathology to aid in the reduction of infant mortality rates to their basic levels.

Blood Pressure

Blood pressure determinations on newly born infants were made with a needle in the umbilical artery and recorded photographically by R. A. Woodbury, M. Robinow and W. F. Hamilton.²²¹ The pressure in the umbilical artery and the brachial arteries were found to be approximately the same. In order to obtain clinical blood pressure readings of similar values, a cuff only 2.5 cm in width was recommended. Cuffs with wider diameters gave results which were too low by 20 to 25 mm. of mercury. In summarizing their results, the authors found that the average blood pressure of newly born infants was 80/46 and tended to increase with age during the first 10 days of life. It was not influenced by such factors as anesthesia of the mother during delivery, the onset of respiration, clamping the cord after birth or the administration of oxygen or carbon dioxide. Slight elevations occurred when the mother had symptoms of toxemia of pregnancy. Crying, dehydration without collapse and the administration of fluids to dehydrated babies tended to elevate the pressure readings. The blood pressures of premature infants were lower than those of the full term group and readings as low as 33/0 were obtained in an infant of 5 months' gestation. With increasing length of

gestation the pressures became more elevated.

Congenital Hypertrophic Pyloric Stenosis

The symptoms and treatment of congenital hypertrophic pyloric stenosis have been reviewed recently by E. J. Donovan.²²² In the group of 143 consecutive cases all but 17 were boys and the first symptoms of the stenosis began in the second to fifth week of life at an average of about 3 weeks. Always, the first symptom was vomiting which either began suddenly or occurred after feeding. The material vomited never contained bile although occasionally blood was present. Peristaltic waves over the epigastrium, passing from left to right, were almost always observed and the palpation of a tumor mass about the size of an olive in the epigastrium just to the right and above the umbilicus was pathognomonic of the lesion.

The author had found little need for x-ray or fluoroscopic examination of these patients, and believed that the diagnosis could be made in most instances from the clinical examination alone. It was his opinion that medical treatment with atropine with thickened feedings was frequently attempted for too long a time and that operation was sometimes postponed until the child's general nutrition was impaired. The operative risk is much less if the baby is in good physical condition and the preparation of the patient by the administration of *blood* and of *saline solution* for a few days to replace the loss of chloride vomited by the infant was very beneficial treatment. Shortly after operation, 15 cc. of water may be offered by mouth and 4 hours later 4 cc. of breast milk diluted with an equal amount of barley water may be given. The feeding can be increased gradually until, at the end of 48

hours, the child may take as much as an ounce every 3 hours. No fatalities occurred in the author's group of 143 patients.

The resuscitation of newly born infants by a mechanical method has been advocated by D. B. Martinez.²²³ He employed a machine which exerted a positive pressure of 13 mm. of mercury and negative pressure of 975 mm. of mercury in alternating sequence. The pressure was exerted through a mask directly over the baby's face very similar to the apparatus used in the administration of gas anesthesia. It was important to remove the mucus from the baby's pharynx before the treatment was started and then either pure oxygen or a mixture of oxygen, 90 per cent, and carbon dioxide, 10 per cent, was employed. As soon as the infant started to breathe, the pressure was automatically shut off so that the infant's own respiratory movements would inhale the gases.

In the treatment of 500 infants by this method, 315 seemed to have received some benefit from the mechanical respirator and 138 were thought to have profited to such an extent that they might have died had this method not been employed. In 24 instances the author believed that no other method would have resuscitated the infants. Autopsies performed on a group of 9 patients showed no evidence of damage caused by the apparatus. Of distinct value in this type of treatment was the ease with which the method could be applied so that the baby would receive the maximum benefit and the least possible injurious effects, even in inexperienced hands.

Epidemic Diarrhea

One of the severe outbreaks of diarrhea in newly born infants which have been reported from various parts of the country recently has been described by

M. Greenberg and B. M. Wronker.²²⁴ The disease occurred over a period of 2 winter months and was confined to 1 part of the hospital only. Diarrhea, loss of weight, dehydration and severe toxic symptoms were characteristic signs and bronchopneumonia and otitis media were frequent complications. A group of 52 infants of a total number of 129 newborn contracted the disease (40 per cent) and 15 (29 per cent) died. No etiologic agent or source of infection could be found, and the epidemic was checked only by the closing of the ward.

In review of the epidemics of diarrhea in the newborn in New York City during the past 4 years, H. Abramson and S. Frant²²⁵ have described the clinical and epidemiological characteristics. The incubation period seemed to vary between 2 and 21 days, the most frequent period being 4 days. Babies 2 to 14 days of age were most often affected. The early symptoms of vomiting, diarrhea, abdominal distention and listlessness were followed within a few hours by severe prostration and evidence of toxemia and acidosis. Babies who survived sometimes developed bronchopneumonia, otitis media or secondary invasion of pyogenic organisms causing septicemia. The illness of a series of 91 infants lasted for 3 to 26 days with a median duration of 9 days. Pathologic changes in the intestinal tracts of these infants were very meager and bacteriologic investigations failed to reveal any definite causative agent. Treatment of the disease was symptomatic, consisting of the administration of fluids, blood transfusions and graduated feedings, but the important factors were the early institution of such therapy. Closing of the wards seemed to be the only method of checking the epidemics.

A statistical study of this disease in 27 epidemics in 19 different hospitals in

various parts of the country has been made by W. H. Best.²²⁶ Several hospitals have had 3 or more outbreaks of the infection with no common factors to account for them. The season of the year seemed to have no bearing on the infection, since the epidemics were equally frequent in winter and summer months. Of a total of 5082 live births, this virulent diarrhea has occurred in 750 (14.7 per cent). Almost half of this number of infants died of the infection. A search for a specific microorganism or virus has given no definite results. Health departments have urged: (a) The reporting of such cases in order to determine the true incidence rates and to detect epidemics early; (b) the improvement of nursery technic so that no infection can reach the baby, and (c) the early closing of any nursery or obstetrical division in hospitals to check the spread of the disease.

Hemorrhagic Disease of Newborn

Hemorrhagic disease of the newborn occurred in 72 infants of a series of 11,303 births reviewed by C. T. Javert.²²⁷ The incidence of anemia, toxemia and syphilis was higher in the mothers of the babies with the hemorrhagic tendency than in the mothers of a control series. The mothers of the affected babies were somewhat older than the control series and had more prolonged periods of labor requiring operative procedures. The group of infants with the bleeding tendency included a larger number of prematures and a larger number of infants requiring resuscitation than did the control series. Bleeding occurred most frequently in the gastroenteric tract, the blood being vomited in 31 instances and appearing grossly in the stools in 12. The skin, umbilical stump, foreskin, vagina, mouth, urine, and eyes showed evidence of bleeding in the remainder of

patients. One-third of the group of infants exhibited the hemorrhages on the first day of life and the great majority bled during the first 4 days of life. Treatment consisted chiefly of *rest* for the infant and the *intramuscular injection of whole blood*. *Transfusion with maternal blood* was recommended when anemia of the infant was apparent unless the mother's condition made it impractical to use her as a donor.

Hepatic Lesions

Hepatic lesions observed at the autopsies of 69 newly born infants have been reviewed by A. S. Price²²⁸. The livers of premature infants generally resembled those of mature infants except that the former have more numerous and larger blood islands, thinner liver cords and smaller sized cells. Passive congestion in the newborn, often associated with congenital heart disease, appeared the same as in adults except that toxic effects were less notable in infants. Simple fatty infiltration was observed in the livers of well-nourished infants to some degree but more marked in those of infants who had been deprived of food either before or after birth. Syphilis produced a perilobular hepatitis with an infiltration of lymphocytes and mononuclear cells in portal canals. Arsenical treatment of the mother produced a toxic manifestation, and acute asphyxia caused a marked congestion of the sinusoids with occasional deposits of hemosiderin. Another type of liver change, not belonging to any of the above categories, was noted by the author in several instances in which there was distention of the hepatic cells, fine deposits of lipid material giving the cells a vacuolated, emulsified appearance and necrotic areas which sometimes obliterated the sinusoids. The central zone apparently became involved first and entire lobules

were affected. Although factors which may have been responsible for this hepatic disease were reviewed, no outstanding etiologic agent could be ascertained. The possibility that rectal ether or some of the barbiturates administered in early stages of labor may cause liver damage must be borne in mind.

Hypoglycemia

A newly born infant with hypoglycemia observed by H. Rascoff, J. S. Beilly and M. Jacobi²²⁹ had a hypertrophy and hyperplasia of the islands of Langerhans. In all of the 9 other cases reported previously in the literature, histologic changes occurred in the pancreas with an increase in the number and size of the islands. In 2 patients, adrenal hemorrhages had also been noted. Of the total number of 10 patients, 5 were prematurely born and the remaining 5, who were full term infants, were larger than average size. The chief diagnostic symptoms of hypoglycemia seemed to be a failure of the infant to respond readily to resuscitation, the occurrence of cyanotic attacks not relieved permanently by inhalations of oxygen and carbon dioxide and, finally, the refusal of the patient to take feedings well. The history of diabetes in the mother should always lead to a suspicion of this condition but a glucose tolerance test of the mother is sometimes necessary to diagnose the condition. Blood sugar determinations should be made on all of the newborn who show the above symptoms and their response to the administration of glucose solutions is rapid when hypoglycemia occurs. The prognosis of the condition is not always good.

Icterus Neonatorum

The cause of icterus neonatorum has been investigated recently by S. G. Ross, T. R. Waugh and H. T. Malloy.²³⁰

Bearing in mind the 3 main factors which have been held responsible for causing icterus neonatorum: namely, excessive hemolysis, impaired function of the liver cells and obstruction in the biliary channels, the authors conducted their investigations along 3 different channels. In the first experiment, newly born infants were examined on the first and fifth day of life in regard to the red cell count, the percentage of hemoglobin, the corpuscular volume percentage and the van den Bergh reaction. In a group of 12 infants, 5 had clinical jaundice and 7 did not, but the reduction in red cell count, hemoglobin and corpuscular volume was about the same in the 2 groups, indicating that the same degree of hemolysis took place in these 12 patients and that excessive hemolysis was not in itself a factor that always caused jaundice.

In a series of 63 infants examined on the fourth or fifth day of life, 22 of whom were jaundiced and 41 normal, none had a direct prompt van den Bergh reaction, but a delayed indirect reaction, and the indirect reaction was distinctly higher in the group with jaundice. Bilirubin was present in the urine in a majority of the jaundiced patients and appeared to be directly dependent upon the concentration of bile in the blood. These tests indicated that the disease was not of the true obstructive biliary type and the biliary channels did not seem to be sufficiently involved to play any important part in the development of jaundice. In a third group of 35 infants, 14 of whom were jaundiced, a study was made of the excretion of bile pigment in the stools and urine during the first 7 days of life. Relatively high amounts of urobilin were excreted in both groups of cases but the amounts were greater in the group that did not have jaundice. From these experiments

the authors concluded that the obstruction of the bile channels was of little significance in the cause of icterus neonatorum and that the basic factors of the condition were the excessive hemolysis and some other mechanism which prevented the excretion of bile pigment. Either the tissues had an increased affinity for bile pigment or, most likely, the liver cells of infants were unable to excrete the large amounts of pigment during the first few days of life. Some functional disturbance of the liver cells due to the increased load thrown upon them would seem to explain the occurrence of many cases of icterus neonatorum and especially would it account for the high incidence of the condition in premature infants.

Jaundice which had been caused by *sepsis* in 2 newly born infants followed by the development of neurological complications of an unusual type has been reported by A. Biemond and S. Van Creveld²³¹. During the neonatal period of life these 2 infants had infections of the umbilical stump and developed severe jaundice and signs of extrapyramidal lesions. Both of the patients recovered from their severe jaundice but died 3 or 4 months later of bronchopneumonia. At autopsy there was found a demyelination and loss of ganglion cells in the globus pallidus and in the corpus subthalamicus on both sides and in 1 instance there was slight icteric staining of the basal ganglia. Liver involvement was noted in both patients, with slight fibrosis in 1 case. Icteric staining of the basal ganglia has frequently accompanied icteric gravis neonatorum, but is much more rare in cases of jaundice due to sepsis. In these 2 infants there was no evidence of erythroblastosis nor was there any family history of icterus gravis or anemia of the congenital type.

Infections

Epidemics of respiratory infections may also occur in nurseries. Such an outbreak has been reported by A. E. Dickie.²³² Seven infants developed symptoms of nasal obstruction, cough and fever. Cyanosis and dyspnea occurred in a few patients and 2 died with evidence of massive pulmonary consolidation. A *Staphylococcus aureus* was found in all of the infected infants and was recovered from the 4 nurses and 1 mother. In 1 instance this microorganism was found in the milk of a mother with a mild mastitis. Upon removal of the carriers and the institution of rigid isolation technique of the nursery, the epidemic disappeared by the end of 1 month. From a review of the literature it seemed that staphylococcal infections are usually tolerated poorly by young infants.

Gonorrheal sepsis following an ophthalmia neonatorum in an infant 4 days of age has been reported by S. J. Hoffman and M. Schneider.²³³ Although the patient had received the regular prophylactic treatment at birth, the eyes became infected with the gonococcus and 12 days later a septic arthritis resulted. The microorganism was isolated from the blood and, at postmortem examination, it was found in the fluid of the right knee joint and in the spleen. The heart was not involved.

Ophthalmia neonatorum has been cured in a very short time by the use of **sulfanilamide**. T. Willis²³⁴ employed the drug in 4 babies in doses of 0.2 to 0.25 Gm per kg of body weight in addition to customary local irrigations of the eyes. The blood concentrations of the drug were observed closely and transfusion therapy was held in readiness to combat any toxic effects of the sulfanilamide.

Acute *suppurative parotitis* is a rare condition in the first days of life. The

infant observed by R. H. Baxter and M. T. MacDonald²³⁵ had been a brow presentation at birth and considerable edema of the face resulted. On the sixth day of life the right parotid gland became swollen and inflamed and a stomatitis was noted. The pus which could be expressed from Stenson's duct contained *B. alcaligenes*. Several incisions on the cheek were necessary before complete drainage and healing took place. A total of 55 cases of infection of the salivary glands, usually the parotid, have been reported previously in the literature. It is the general opinion of most observers that the infection is an ascending one from the mouth.

Two cases of suppurative parotitis were described in newly born infants by H. Bloch and B. L. Pacella.²³⁶ One infant was 4 days old and the other 6 days when the swelling of the parotid was first noted. Incision and drainage were necessary in both instances and the culture of the pus obtained from 1 gland showed the presence of a *staphylococcus albus*. These infants were the only 2 with this condition in a series of 19,550 consecutive births.

Intracranial Hemorrhage

The symptoms and clinical findings of a series of 126 newly born infants with intracranial hemorrhage have been summarized by W. S. Craig.²³⁷ Autopsy proof of the condition was obtained in all of these patients. Subdural hemorrhages occurred in 62 infants, the majority of whom were full term infants delivered with the aid of instruments. Asphyxia and an unnatural alertness with an expression of anxiety, followed by sporadic periods of improvement, were common early symptoms. Convulsive movements, in-co-ordinated eye movements, muscle spasticity, and hyperactivity of

reflex action frequently occurred. Hemorrhage below the tentorium often caused rigidity of the neck and deep cyanosis. Subarachnoid hemorrhage was noted in 36 patients with very few definite symptoms but was often associated with frailty of the infant. The symptoms were often delayed in their appearance until later in the infant's life. Intraventricular hemorrhage occurred in 22 infants and was accompanied by symptoms of a sudden onset most frequently in premature infants, and a cry and facial expression denoting pain. Rigidity of the neck and retraction of the head often occurred and death usually followed very rapidly. The removal of cerebrospinal fluid gave only temporary relief. Hemorrhage into the brain substance was noted in only 6 infants, all of them large babies and delivered after a prolonged labor. The facial expression was one of fear and they slowly declined in health with the development of muscular flaccidity and weakness. The fontanel in a baby with intracranial hemorrhage bulged sometimes but more often it felt full and spongy. Such factors as toxemia or infection of the mother, and instrumental delivery have an influence on the occurrence of such hemorrhages and careful obstetric and nursing care seemed to be essential for the prevention of the lesions.

Attention has been called to some of the predisposing factors of intracranial injury of premature infants by W. E. Studdiford and H. P. Salter.²³⁸ In a series of 249 premature deliveries, the condition seemed to occur most frequently when the second stage of labor was prolonged and was less common when episiotomy was performed. The careful management of the first and second stage of labor was considered to be a major factor in the prevention of intracranial injuries of the infant.

Prematurity

Factors which influence the *mortality of premature infants* have been surveyed recently by B. B. Breese, Jr.,²³⁹ from a study of the records of 987 infants whose weights were less than 2500 Gm. (5.5 pounds) at birth. The conclusion was reached that weight was the most important factor in the prognosis of the premature infant. Other conditions which may have had an influence on mortality rates were found to be hydramnios, and breech delivery. The age of the mother had no effect except in the case of women over 40 years of age at the time of the delivery of their infants and this seemed to have an unfavorable effect. Induction of labor, Cesarean section and forceps deliveries did not add to the risk of the premature's life. Ether, administered to the mother during delivery, seemed to be a safe anesthetic, but morphine was a dangerous drug in its effects on premature mortality. Prolongation of gestation seems to be necessary to reduce the incidence and mortality of prematurity but often the health of the mother will not permit this to be accomplished and, therefore, adequate methods of handling and treating premature infants are still important requisites.

Further indication that premature infants who survive the first few months of life tend to develop mentally and physically as well as full term infants has been corroborated by the observations of K. Bae-dorf.²⁴⁰ He examined 27 children who had weighed between 1050 and 1700 Gm. at birth and now were 5 to 17 years old. Their rate of development in both height and weight compared favorably with normal growth curves. Their mental status, judged from the history obtained from the parents, and school teachers, and from Binet-Simon intelligence tests, indicated an average mental development.

In the group were 5 children of the lower mental levels but this seemed to be no more than should be expected from similar samples of population and such a small number might be attributed to hereditary or traumatic etiology.

The administration of *thyroid extract* to premature infants has produced favorable results in the series of patients observed by A. Moncrieff.²⁴¹ Doses of $\frac{1}{20}$ grain of the thyroid extract per pound (6 mg. per kg.) of body weight were administered daily for a maximum period of 2 weeks. Thirty-two infants served as the experimental group and an equal number of comparable weight were employed as a control group. The infants receiving the medication seemed to gain less weight than the untreated patients, probably because of the stimulation of metabolism produced by the thyroid substance. The temperatures of the treated group, however, were held at higher average levels as a rule than those of the control series. Most important of all, the mortality rate of the babies receiving thyroid extract was only 6 per cent as compared with 17 per cent among the control series.

The relative values of *human and cow's milk for the feeding of premature infants* has been investigated by H. H. Gordon, S. Z. Levine, M. A. Wheatley and E. Marples.²⁴² In 6 premature infants, the nitrogen retention was approximately the same when the 2 types of milk were fed in equivalent caloric amounts, but larger amounts of nitrogen were utilized by prematures than by full term infants. When the nitrogen content of a feeding was increased without increasing the caloric value, larger amounts of nitrogen were retained but utilization percentages dropped. Fat seemed to be absorbed in smaller relative amounts by prematures than by full term infants.

A new food for prematures has been recommended recently by A. V. Stoesser and E. Johnson.²⁴³ It consisted of 40.6 per cent skimmed cow's milk, 10.1 per cent of calcium caseinate, 17.5 per cent olive oil, 31.7 per cent of a maltose and dextrin preparation and 1 per cent of halibut liver oil. This feeding seemed to be tolerated better by a group of 80 premature infants than was an evaporated milk mixture by a control series of 71 premature babies. For a group of premature infants weighing more than 2000 Gm., this diet seemed to be more effective than breast milk or evaporated milk formulas.

Skin Lesions

Various methods of caring for the skin of newly born infants have been compared over a period of 6 years by H. N. Sanford.²⁴⁴ The common eruptions were those due to irritation which produced the erythematous macules and papules, the pustular type which included all forms of impetigo and pemphigus neonatorum and, finally, the pustular eruptions accompanied by exfoliation which were the most rare forms. In the previous literature the author found that the incidence of pustular eruptions was reported to vary from 00 to 6 per cent of newly born infants. In his own series of 3500 newborn, the routine care of the skin had included the use of 2 per cent *ammoniated mercury* at birth followed by *daily baths* with water and castile soap, baths with olive oil, or mixtures of olive oil and mineral oil, or commercial preparations. Since none of these methods had any marked influence in reducing the incidence of skin lesions, the final method employed was that of total neglect of the skin of the infant for the first 9 days of life except for the removal of excess blood at birth. Pustular lesions practically disappeared in the nursery

with this last form of treatment with only 1 infant (0.2 per cent) of a group of 609 developing pustular lesions. There was very little seasonal variation in the incidence of either the irritative or pustular types of lesions and an increased frequency of irritations did not lead to an increased frequency of pustules. The cause of either the irritative or pustular eruptions is not definitely known. Since most of the erythemas occurred during the first 3 days of life, when the infant was receiving little or no breast milk, the author concluded that allergic reactions from food were probably not the cause of the eruptions but might be the result of handling and of irritation from linen from which excessive amounts of alkali or acid had not been removed in washing. In spite of all precautions approximately 10 per cent of the infants developed some type of irritative lesion.

The *prevention* of the pustular eruptions seemed to depend upon the *improvement of nursing technic, aseptic care of the baby, the isolation of infected infants*, and, most important of all, the *avoidance of irritation* from baths and oiling by leaving the skin absolutely alone.

Similar results have been reported by L. H. Smith,²⁴⁵ who has observed 1734 newly born infants who received no cleansing of the skin during their stay in the hospital. The buttocks were cleansed with warm water after stools had been passed. Within 12 hours after birth, the infants' skin became clean with a complete disappearance of the vernix caseosa except possibly under the arms and in the groin. The incidence of skin irritations and pyoderma greatly decreased under this régime.

Two epidemics of *pemphigus neonatorum* from which staphylococcus aureus was isolated have been described by F. D. Hart.²⁴⁶ In 1 case a purulent rhinitis of

an infant and, in another, a mastitis of a mother seemed to be the source of the infection since the same microorganism had been isolated from these lesions.

The *treatment* of pemphigus was limited to the application of *antiseptic solutions*, such as *mercuochrome* and *potassium permanganate*. *Ultraviolet radiation* has been suggested as a beneficial form of therapy. Prophylaxis of the disease by rigid aseptic technic is highly important since the mortality rates from the infection are high, especially in premature infants.

A mouth infection resembling thrush in its appearance but of undetermined etiology occurred in epidemic form in 46 of a series of 50 infants observed by L. H. Douglass.²⁴⁷ The untreated patients recovered more rapidly than those who received local applications of perborate of soda or gentian violet solutions. None of the infants died, but the epidemic was checked only by the closing of the ward for 10 days, during which time it was thoroughly cleaned and aired.

The term *sclerema neonatorum* has been reserved for the description of small areas of subcutaneous fat necrosis which occur in localized areas in the skin and subcutaneous tissues in newborn babies during the first few weeks of life. The lesions usually become soft and sometimes progress to cystic forms but the general health of the infant is not impaired. An instance of this disease has been described recently by J. F. McIntosh, T. R. Waugh and S. G. Ross.²⁴⁸ Several small areas of induration which developed in the scapular region and upper part of the arms subsequently discharged a yellowish semifluid material. Histological examination showed that changes had occurred in the fat cells of the subcutaneous tissue and that crystals were very numerous but no lipase was present in this material. The areas were sur-

rounded by fibroplastic proliferations and cellular exudate. In general, the subcutaneous fat of a newborn child has been found to be low in olein content but the occurrence of the subcutaneous fat necrosis seems to be due to a change in the physical properties of the fat and not in its chemical state. It is assumed that obstetrical trauma is the predisposing factor.

Tetany

The subject of tetany of the newborn has been reviewed recently by H. Bakwin²⁴⁹. Attention was called to the fact that subdural hematoma or forms of meningitis in the newborn can produce symptoms of convulsions and carpopedal spasms which are very similar to those of tetany. The diagnosis of tetany is made by finding a serum calcium content below 8 mg per cent. Such a tetany may be caused by a disturbance of parathyroid secretion, the ingestion of large amounts of phosphate, a deficiency of vitamin D or by obstruction of the intestinal tract. Other forms of tetany without a lowered calcium content of the blood may be produced by alkalosis, resulting from the ingestion of large amounts of sodium bicarbonate, from the vomiting of acid in pyloric obstruction or from hyperventilation. These latter forms of tetany are extremely rare in the newborn.

In normal infants the serum calcium tends to fall from figures of 11 mg at birth to 9.8 mg by the fifth day and after this time there is a slight rise to slightly over 10 mg per cent. The

serum phosphorus rises during the same time to figures of 6.1 to 6.8. It has seemed probable that the decline in calcium is due to a temporary decrease in the parathyroid secretion of the infant and that the phosphorus plays an important part in the production of tetany in the newborn. The mothers probably develop an increased parathyroid secretion which is suddenly cut off from the baby at the time of its birth.

In experimental animals, tetany may be produced by the administration of phosphates and, conversely, the disease may be prevented by the restriction of phosphates in the diet. It is possible that excessive amounts of phosphate tend to inhibit the patient's absorption of calcium by forming an insoluble calcium phosphate in the lower part of the intestinal tract.

Tetany in the newborn may be produced in part by the ingestion of large amounts of phosphorus, which is abundant in colostrum and present in excessive amounts in cow's milk. The starvation period of the first few days of life may also tend to increase the amount of phosphorus liberated within the body. Phosphorus is excreted in only very small amounts in the urine of the newly born baby. The combination of events during the first days of life in which the serum calcium decreases and the phosphorus increases either from starvation or from the excessive ingestion in the form of cow's milk may be the explanation for the occurrence of most cases of tetany at this age.

NUTRITION AND NUTRITIONAL DISEASES

By WALDO E. NELSON

Vitamin A—Clinical studies to determine the adequacy of the vitamin A content of the average infant diet have been

carried out by J. M. Lewis and L. H. Barenberg²⁵⁰. Fifty-one infants were given a diet which contained approxi-

mately one-fourth the vitamin A content of the average diet and 53 infants were given a diet which contained from 4 to 8 times the number of vitamin A units in the average diet. These infants were observed for an average period of between 6 and 7 months, and a comparison of the nutritional status and the incidence of infection of the 2 groups was made. The authors were unable to detect any difference in the nutritional status or the susceptibility to infection between the 2 groups of infants. They concluded that the average diet of infants contains at least 4 times as many units as the minimal requirement, as judged by the nutritional state of infants and their resistance to infection. They tend to agree with Guilbert that the requirement of vitamin A, in contradistinction to that of vitamin D, depends on body weight rather than on rate of growth. Thus adults would require many more units of vitamin A than do children to protect them against night blindness. Similarly, it seems probable that children require a greater number of vitamin A units than do infants to permit normal dark adaptation.

Vitamin B₁—On the basis of controlled feeding experiments in infants, M. W. Poole, B. M. Hamil, T. B. Cooley and I. G. Macy²⁵¹ state that vitamin B₁ in the diets of infants aids in promoting a more stabilized growth and a greater nutritional stability. One group was given 90 to 100 more Sherman-Chase units of vitamin B₁ per day than a control group of infants. Various observations and measurements were made at monthly intervals and included anthropometric measurements, roentgenograms of the long bones and hematologic studies. The efficiency of utilization of milk became superior after the 126th day of life for the infants who received their milk fortified with vitamin B₁.

While the hemoglobin values of the vitamin B₁ group did not show a higher average level except in the later weeks of observation, they did not fluctuate as widely.

E. Robb, E. M. Vahlteich, and M. S. Rose²⁵² have studied the vitamin B₁ content of the dietary of nursery school children. On the basis of their studies, they state that an adequate amount of vitamin B₁ will be furnished if at least 40 per cent of the total number of calories is derived from milk, 18 to 20 per cent from cereals, with at least half the cereal calories from whole-grain products in which the vitamin B₁ has not been to any considerable extent destroyed by heating in manufacture, and 16 to 22 per cent from fruits and vegetables. In addition 3 to 4 ounces of orange juice or its equivalent in tomato juice should be provided daily for their vitamin C content. No accurate prediction can be made as to the number of units such a diet will yield owing to the natural variability in foods and the losses which may occur in cooking or in commercial preparation. It was noted that the vitamin B₁ content of the diet could be increased with little, if any, extra cost by the use of whole wheat bread and of a whole wheat cereal reinforced with wheat germ.

From feeding experiments carried on for a period of 32 weeks, F. W. Schlutz and E. M. Knott²⁵³ conclude that the optimum ingestion of vitamin B₁ is approximately 400 to 500 international standard units per day.

The experimental observations of A. L. Daniels²⁵⁴ indicate that commercial evaporated milk contains about 60 per cent less vitamin B₁ than an equivalent amount of raw summer milk.

Further data have been published by L. J. Harris, P. C. Leong and C. C. Ungley²⁵⁵ concerning the efficacy of meas-

urement of vitamin B₁ in human urine as an index of nutritional level. The authors conclude that the urinary excretion furnishes a useful measure of the state of nutrition of the subject with regard to vitamin B₁. They suggest the following provisional standards: A "resting level" of excretion of 10 to 20 I. U. and an excretion of 30 I. U. or more after the standard test dose (350 I. U.) are indicative of average or normal nutrition. Excretions of less than 10 I. U. (resting level) and 15 I. U. (after test dose) seemed sufficiently removed from the average range to be classified as subnormal. Polyneuritic symptoms of nutritional origin have been found to be associated with resting levels of 3.5 I. U. and under and with low responses to test doses.

These measurements are based on data obtained from rat experiments. The authors are investigating a chemical process for estimating vitamin B₁ in urine and it is possible that this method may provide more accurate results.

Vitamin B₂.—A method for the estimation of vitamin B₂ in human urine has been described by M. K. Maatra.²⁵⁶ The urine is fed to rats who have been fed during a preliminary period on a diet adequate except for vitamin B₂. The growth response of the rats is taken as an indication of the presence of vitamin B₂ in the urine.

Vitamin C.—According to M. van Eekelen and M. Hememann,²⁵⁷ ascorbic acid in urine cannot be determined reliably by direct titration with 2,6-dichlorophenol-indophenol. Reducing substances other than ascorbic acid, present in urine, also decolorize this indicator. They can be removed by precipitation with mercuric acetate. The excretion of these interfering substances can increase considerably, under various conditions, and independently of that of the vitamin.

The observations of J. M. Faulkner and F. H. L. Taylor²⁵⁸ indicate that the output of ascorbic acid in human urine is dependent upon the serum level of the vitamin. Ascorbic acid thus appears to be a threshold substance with a critical level of excretion in the vicinity of 1.40 mg. per 100 cc. of serum.

C. P. Manahan and N. J. Eastman²⁵⁹ are in agreement with Braestrup that the ascorbic acid concentration in fetal blood is regularly almost 3 times that of maternal blood. Raising the concentration of ascorbic acid in the maternal blood by the antenatal administration of orange juice raises concomitantly the concentration in the fetal blood, the ratio between the concentration in the 2 bloods remaining similar. The authors suggest that the high relative concentration of ascorbic acid in fetal blood results from a selective action on the part of the placenta in respect to vitamin C.

A 5-hour test for the determination of vitamin C saturation has been described by I. S. Wright, A. Lilienfeld and E. MacLennan.²⁶⁰ The test is performed as follows. Breakfast is omitted and the bladder is emptied and this specimen of urine is discarded. One gram of ascorbic acid in 10 cc. of physiologic solution of sodium chloride is injected intravenously. All of the urine voided during the first 5 hours, including a specimen voided exactly at the end of the fifth hour, is collected. Titration is done as soon after the 5-hour period as possible to avoid undue loss of the vitamin. According to the authors 500 mg. or more of the 1 Gm. dose is normally excreted in the first 24 hours and 400 mg. of that is excreted in the first 5 hours.

The vitamin C content of the blood, of the spinal fluid and of the 5-hour urinary excretion after a 1 Gm. intravenous test dose of ascorbic acid was determined for 138 patients by H. Wortis, J. Liebmann,

and E. Wortis.²⁶¹ A blood content of vitamin C above 0.7 mg. per 100 cc. was almost invariably associated with a normal spinal fluid content and a normal urinary excretion test for vitamin C. A blood content of vitamin C below 0.4 mg. per 100 cc. was almost invariably associated with a subnormal spinal fluid content and a subnormal urinary excretion test. In these ranges the blood was an adequate and accurate index of the state of vitamin C nutrition. In the intermediate subnormal range for blood (from 0.4 to 0.69 mg per 100 cc.), it is recommended that all available tests be used, including clinical evaluation of the patient. The authors emphasize that scurvy is a clinical entity and its diagnosis cannot be made by the vitamin C determinations alone.

A clinical study to determine the efficiency of an intradermal dye test for vitamin C deficiency has been carried out by H. G. Poncher and C. H. Stubenrauch, Jr.²⁶² The test as described by Rotter and by Portnoy and Wilkinson consists in the intradermal injection of 2,6 dichlorophenol-indophenol. It was presumed that the speed of reduction of this dye in the tissues as characterized by the rate of decolorization of its blue color would indicate the saturation of the tissue with vitamin C. Poncher and Stubenrauch's results do not confirm the conclusions of Rotter or of Portnoy and Wilkinson in that their data with the intradermal test did not correspond with the cevitamic acid blood level. They conclude that the test in its present form is not of clinical value.

The relation of ascorbic acid ingestion to mineral metabolism in children has been studied by A. L. Daniels and G. J. Everson.²⁶³ No influence on calcium, phosphorous and magnesium retentions was observed when the ascorbic acid ingestions were between 27 and 12.5

mg. per kg. of body weight. In a controlled ascorbic acid balance study in which the ascorbic acid retentions were shown to be below the physiologic minimum, there was found to be no appreciable difference in the average retentions of calcium, phosphorous and magnesium.

Ascorbic acid appeared to be related to nitrogen metabolism. The average nitrogen retention at levels of ascorbic acid ingestion below the physiologic minimum were found to be lower than when the children were receiving adequate amounts as shown by the ascorbic acid retentions. Ascorbic acid ingestions in excess of the physiologic requirements, however, did not further increase the nitrogen retention.

A. D. Kaiser¹⁴⁷ states that while there is some evidence that the rheumatic patient needs increased amounts of vitamin C, its administration in adequate amounts will not prevent rheumatic infection or promptly bring about recovery. He does not believe that vitamin C deficiency is a significant etiologic factor in rheumatic infection. However, there is sufficient clinical evidence to stress the importance of the regular administration of adequate amounts of vitamin C to all patients suffering from rheumatic disease.

J. F. Rinehart, L. D. Greenberg, M. B. Olney and F. Choy²⁶⁴ have also found that the ascorbic acid content of the blood plasma is uniformly low for patients with acute rheumatic fever. Furthermore, the majority of their patients, convalescent from rheumatic fever or with inactive rheumatic fever, also had low blood plasma values. In contrast to Kaiser's opinion they suggest that vitamin C deficiency may be of etiologic significance. That children with active tuberculosis require more vitamin C than do well children is also apparent from the

work of various authors, among them being W. W. Jetter, and T. S. Bumalo.²⁶⁵ In the study of these authors all of 37 tuberculous children showed a decreased urinary excretion of vitamin C on a daily ration of 55 to 65 mg. Their average daily excretion was 5.7 mg. as compared with a 29.2 mg. average of 25 normal control children. In general, the greater the severity of the tuberculous process, the lower the excretory figures. More extensive data are supplied by J. M. Faulkner and F. H. L. Taylor²⁶⁶ to show that the amount of vitamin C in the diet necessary to bring the serum level and the urinary output to normal values in the presence of infection in general is far greater than the normal requirement.

Scurvy—A case of scurvy in an infant 6 months of age with hemorrhage into the brain, the dura and retina is reported by E. Shapiro and S. Hurwitz.²⁶⁷

Active scurvy in an infant 21½ months of age, who had received 4 drams of orange juice daily, starting at the age of 2 months is reported by E. A. Hagmann.²⁶⁸ The scurvy remained active in spite of orange juice and ascorbic acid administered orally. It is of interest that after 3 days of intravenous medication with ascorbic acid, all signs of active scurvy disappeared. The author suggests that there may have been a temporary faulty absorption from the gastroenteric tract. After discharge from the hospital the infant received from 2 to 3 ounces of orange juice daily and showed no further evidence of scurvy.

Vitamin D—Rickets—An attempt to determine the incidence of rickets in 2 far western cities, Portland, Oregon, and San Diego, California, has been made by C. U. Moore, J. L. Brodie and A. J. Thornton, A. M. Lesem and O. B. Cordua.²⁶⁹ A large group of children, 5 years of age, were examined in each

city. The children were chosen from different sections of the city so that they would represent a typical cross section of all social classes. More than 90 per cent of the children examined had 3 or more signs of rickets. On the basis of their data, the authors conclude that, under modern living conditions, abundant sunshine does not furnish adequate protection against rickets and advise universal adoption of some inexpensive dietetic antirachitic preparation.

The adequacy of percomorph liver oil as an antirachitic agent has been tested by R. L. Roddy, E. K. Rose, P. J. Hodes and J. C. Gittings.²⁷⁰ In 16 infants with rachitic osseous changes at the start of the study, 14 were completely healed and 2 showed incomplete healing after a period of 41½ months. Of 84 nonrachitic infants, 63 (75 per cent) were completely protected over the same period of time. Eleven premature infants were completely protected or healed. The rickets which developed in the course of this study was of the mildest type and apparently of no clinical significance. A daily dose of 5 drops of percomorph liver oil appeared to afford as much protection as ten drops.

The antirachitic efficiency of irradiated cholesterol has been studied by J. S. Hood and I. Ravitch.²⁷¹ The irradiated cholesterol was dissolved in corn oil and was administered to 177 nonrachitic infants varying in age at the beginning of the observation from 1 to 5 months. The period of study covered from 5 to 7 months. The infants were divided into 3 groups and were given, respectively, 350, 675, and 950 I. U. of vitamin D as irradiated cholesterol. However, the authors estimated that these were minimal doses and that in many instances the daily dose may have been increased as much as 25 to 30 per cent. In only 2 infants, 1 white and 1 colored,

did rickets develop, which was in each instance of an extremely slight degree. Both infants were in the lowest dosage group.

The curative effect of irradiated cholesterol in oil was observed in 41 infants with mild rickets and in 5 infants with severe rickets. The authors state that their experience is too limited to permit conclusions of a comparative nature based on past experience with cod liver oil or viosterol; however, they have gained the impression that irradiated cholesterol was a powerful antirachitic substance, fully the equal of viosterol or cod liver oil, unit for unit, and perhaps superior.

Further studies to determine the antirachitic value of irradiated, evaporated milk in infants have been conducted by M. Rapoport, E. Krick, and J. Stokes, Jr.²⁷² They had previously shown that irradiated, evaporated milk was an adequate antirachitic agent for hospitalized infants, both white and negro. In this study they have observed the antirachitic effect of irradiated evaporated milk from December to May in outpatient practice. There were 97 nonrachitic infants, 50 negroes and 47 whites. Of these, 82 remained completely free from rickets, 14 developed mild rickets which disappeared during the 5-month period of observation, and 1 developed mild rickets which did not disappear. They thus conclude that irradiated evaporated milk is an effective prophylactic antirachitic agent under the ordinary conditions of outpatient practice.

An unusual instance of rickets resistant to vitamin D therapy in a boy, 16 years of age, is reported by F. Albright, A. M. Butler, and E. Bloomberg.²⁷³ The changes in the calcium and phosphorous metabolism and the histologic data indicated that the condition was true rickets and not some other condi-

tion resembling rickets. The resistance to vitamin D therapy was not due to failure to absorb vitamin D, since crystalline vitamin D injected intravenously and irradiation from an ultraviolet ray lamp were ineffective. With massive doses of vitamin D, such as from 150,000 to 1,500,000 U.S.P. units daily by mouth (from 15 to 150 cc. of viosterol or from 15 to 30 cc. of crystalline vitamin D in propylene glycol), the disorder of metabolism was corrected and healing of the rickets took place. It is pointed out that it is necessary to observe such a patient carefully, lest, with healing of the rickets, too large doses of vitamin D will produce hypervitaminosis. It is believed that the disturbance in this patient is not a deficiency disease like ordinary rickets but rather due to an intrinsic resistance to the antirachitic action of vitamin D.

Further data confirming Gerstenberger's contention that the liver plays an important rôle in the antirachitic function of vitamin D are presented by W. Heymann.²⁷⁴ He has shown experimentally that the antirachitic efficacy of vitamin D in rachitic rats was greatly diminished when obstructive biliary cirrhosis of the liver was produced by operation, and it was inhibited when the liver was damaged by administration of carbon tetrachloride. Since in each instance vitamin D was given by intramuscular injection, the possibility that intestinal absorption might have played a rôle can be ruled out. Administration of Drisdol instead of viosterol in oil showed that the diminution in the curative effect of vitamin D obtained in the jaundice group could not be explained by the inhibition of the absorption of vitamin D at the site of injection. The assumption that jaundice injures the osteogenetic cells to an extent that might impair their property of calcifying was

refuted by the observation that parental administration of a phosphate solution produced healing in jaundiced, rachitic rats as easily as in those not jaundiced. Thus the author concludes that the only interpretation possible is that the decreased antirachitic efficacy

the rachitogenic diet in sufficient amounts, furnished protection against the development of rickets. When equivalent quantities of the acids and salts were fed, it was found that the salts were slightly more effective than the corresponding acid. Animals placed on a rachitogenic

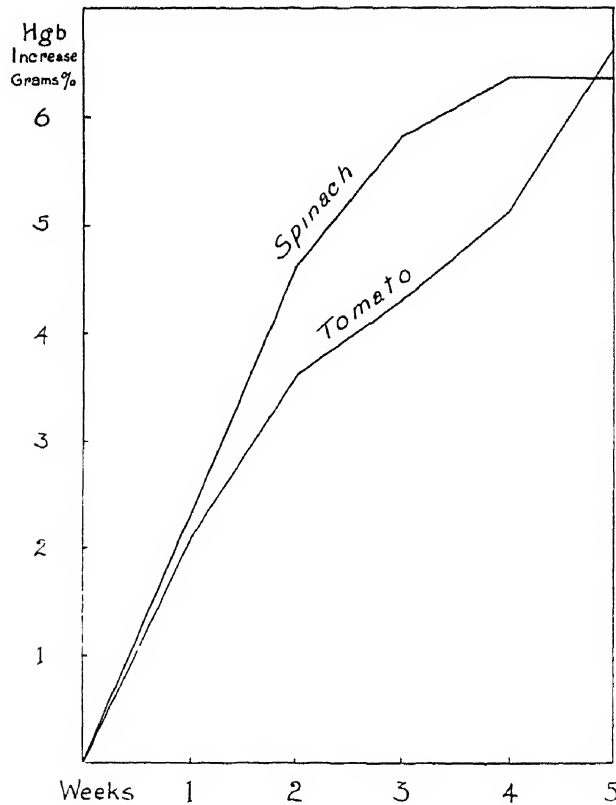


Fig 16—Hemoglobin regenerating power of approximately equal amounts of fresh cooked spinach and canned tomatoes. Hemoglobin regenerating power on anemic rats of the daily feeding of 461 mg of dried cooked spinach (7.9 gm fresh cooked spinach), containing 0.31 mg of total iron. 378 mg of dried cooked tomatoes (9 gm canned tomatoes), containing 0.09 mg of total iron. The anemia-producing diet of the animals contained an adequate supply of copper (J. Pediat., Sept., 1937).

of vitamin D was due to impairment of hepatic function.

B. Hamilton and M. M. Dewar²⁷⁵ have shown that citric and tartaric acids and the sodium salts of these acids have a marked tendency to prevent the development of rickets in rats on a rachitogenic diet and to cause healing when administered to rachitic animals. Sodium citrate, sodium tartrate and sodium bitartrate, when incorporated in

diet until severe rickets developed and the acids or salts then administered along with the diet for periods of 5 to 10 days evidence of marked healing.

Protein — From balanced studies measuring the caloric and protein requirements and basal metabolism in children from 4 to 14 years of age, J. W. Maroney and J. A. Johnston²⁷⁶ state that with calories adequate for growth, intakes of protein representing 15 per

cent of the total calories appear to be optimal. Amounts greater than 20 per cent were usually productive of pallor, loss of appetite, abdominal discomfort and sometimes vomiting. With less than 15 per cent of protein, a negative nitrogen balance or depression of basal metab-

and S. H. Jackson²⁷⁷ the nutritional value of spinach is greatly overrated and in contrast sufficient prominence has not been given to the nutritional value of canned tomatoes.

Their data indicate that cooked spinach and canned tomatoes are approxi-

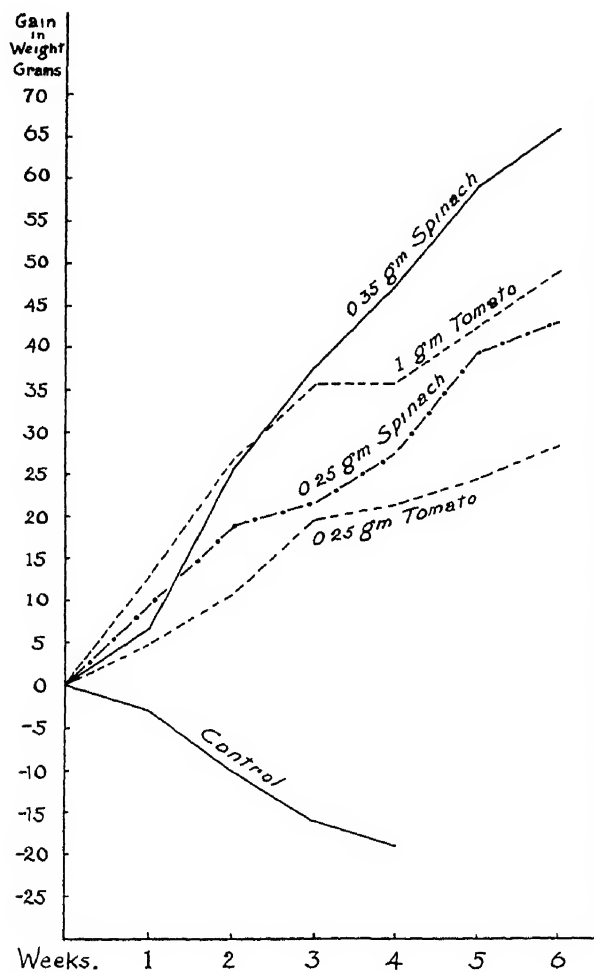


Fig. 17—Weight gain in vitamin A depleted animals, produced by cooked spinach and canned tomatoes (J. Pediat., Sept., 1937)

olism was frequently observed. They confirmed the saving effect of fat and carbohydrate on protein and suggest that this constitutes an argument for recording the protein requirement in terms of the percentage of calories rather than in grams per unit of weight.

Vegetables—According to F. F. Tisdall, T. G. H. Drake, P. Summerfeldt,

materially of equal value as a source of iron for the prevention and cure of nutritioned anemia in spite of the fact that the total iron content of cooked spinach is more than 3 times greater than that of canner tomatoes (Fig. 16).

Spinach, although it contains 0.19 per cent calcium, an amount 20 times greater than found in tomatoes, actually tends

to produce a negative calcium balance. In contrast, the retention of the calcium in cooked tomatoes is excellent.

The vitamin A content of cooked spinach is approximately 4 times as great as that of canned tomatoes (Fig. 17)

The vitamin B₁ content of cooked spinach is approximately one-half that of cooked tomatoes (Fig. 18)

carded in the preparation of tomatoes for consumption

The possibility that spinach because of its high oxalic acid content might have a deleterious effect upon calcium metabolism in man has been suggested by several observers. P. Bonner, F. C. Hummel, M. F. Bates, J. Horton, H. A. Hunscher and I. G. Macy²⁷⁸ have

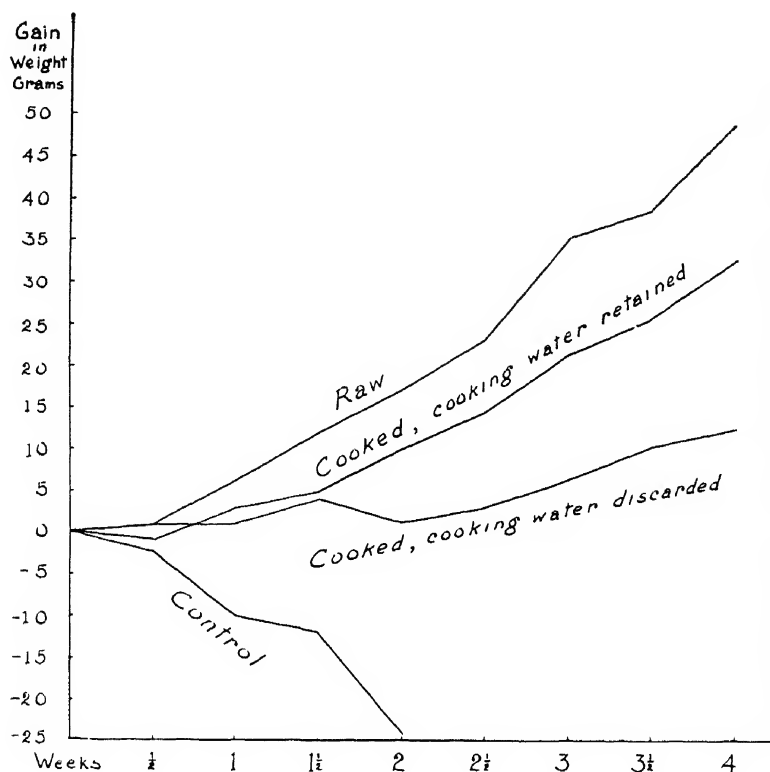


Fig. 18—Loss of vitamin B₁ during the cooking process of spinach (J. Pediat., Sept., 1937)

The vitamin C content of cooked spinach is less than one-quarter that of canned tomatoes

The vitamin D content of cooked spinach and canned tomatoes is negligible

Many of the food elements of spinach may be lost in the discarded cooking water, even when the cooking is carried out under ideal home conditions. If these conditions are not observed, the loss may be greatly accentuated. On the other hand, there need be no water dis-

studied the influence of a daily serving of spinach or its equivalent in oxalic acid upon mineral utilization of children. Their data indicate that there is no cumulative toxic or untoward effect either in the average daily retention or in the progressive storage of nitrogen, calcium, and phosphorus either during the period of consumption of spinach and oxalic acid or during the control period immediately following. The supplementation of an already adequate diet with a gen-

erous serving of spinach daily, for as long as 40 consecutive days, did not change the rate of calcium storage in growing children when calcium intake was adequate to cover the precipitating effect of the oxalic acid and to provide for the fluctuating growth needs. They conclude that spinach is not harmful even in servings of 100 Gm. daily, at least in preadolescent children.

Selection of malnourished children—A method for the detection of school children who grow poorly during the school year has been suggested by C. E. Turner and A. Nordstrom.²⁷⁹ The employment of height-weight-age tables and of the various indices based upon several body measurements has not proved entirely practical for the detection of children who are in need of

medical attention. Since disease, poor nutrition, and lack of rest interfere with growth, the authors suggest the selection of children on the basis of failure in growth. The authors propose using intermittency in growth as a practical screening procedure. They advise the weighing of children every month of the school year except June and recording of intermittency when there is no gain or a loss for each month of 3 successive months. School experience has shown that it is worth while for the teacher, the nurse, and the school doctor to investigate the cases of children who have stopped growing for long periods—investigating (a) poor habits or recent illnesses, because of which they may need a modified program, and (b) serious physical defects which need correction.

PARASITIC DISEASES

WALDO E. NELSON, M.D.

Pinworms

In a discussion of the efficacy of the various methods advocated for the treatment of pinworms, W. H. Wright and E. B. Cram²⁸⁰ emphasize the necessity of having a reliable method of diagnosis. They state that the ova are not deposited in the intestinal canal, as are those of many other worms, but are expelled by the gravid female after it has migrated out of the anus and upon the perianal region. For this reason the examination of samples of stools for pinworm ova is a haphazard and unreliable method of diagnosing pinworm infestation. The stools of the vast majority of patients with pinworms will not reveal pinworm eggs, and although the occasional positive findings are significant, the negative findings do not indicate the existence or absence of infestation. The authors

advocate the employment of an anal swab or scraper of the type described by M. C. Hall.²⁸¹ This swab is made of cellophane. They state that a satisfactory anal swab or scraper must be of such material that pinworm ova, if present, will regularly adhere to it, that it must be in such form that it can be transported from the hospital, clinic or home to the laboratory without loss of parasite material and without danger that infective material will be transferred to other persons, that it must be of such design that it can be examined accurately in the laboratory with a minimum of handling and effort, and that, in the interest of economy, its base should be constructed of such heat-resisting material that it can be sterilized and used repeatedly or of such cheap material that it can be used and discarded.

No method of treatment at present available is entirely satisfactory, since there is no known anthelmintic which in single doses will remove all the worms from every patient or all the worms from nearly every patient and which is sufficiently safe for use with persons of all ages. In the authors' investigations **tetrachlorethylene** comes closest to meeting these specifications for single dose treatment. Tetrachlorethylene is a much safer drug than oil of chenopodium or carbon tetrachloride and has a sufficient margin of safety to permit its administration to young children. From the standpoint of water solubility, it is in a favorable position since it is of great value for the elimination of certain nematodes located in the small intestines and yet, theoretically, is sufficiently insoluble (1 part soluble in 5400 parts of water) so that it is probably carried in considerable concentration into the large intestine and is capable of acting on worms located there. Although tetrachlorethylene usually is administered in a solution of sodium or magnesium sulfate, it was found that by administering it in a suitable dose of magnesium citrate solution, the objection of young children to the taste of the sulfate solution was avoided. **Hexylresorcinol administered orally and by enema** or by enema alone appears to be of definite value in some cases of oxyuriasis. In young children the authors have employed the drug in enemas only and have had excellent results in clearing up the infestations in some instances. Other cases did not respond so satisfactorily. If enemas are employed, they should be given properly and so spaced that the gravid females are removed before their migration through the anal canal. To be most effective, they should be given with the patient in the knee-chest position with the buttocks elevated. This position

should be maintained for several minutes after which the patient should lie on the right side to allow gravitation of the fluid across the transverse colon and into the ascending colon.

The employment of enemas is particularly indicated in the case of children under 4 years of age, since sufficient work has not yet been done to establish both the safety and the efficacy of any anthelmintic administered orally to children of this age. It has been the practice of the authors to employ hexylresorcinol enemas only when the treatment can be given by a trained nurse. Under other conditions, **soapsuds enemas** are recommended. So far results obtained with hexylresorcinol enemas have been more promising than those obtained with soapsuds enemas.

The authors have not found that anal ointments have any appreciable value in destroying the tadpole larva within the egg and thus preventing reinfestation. Such ointments do have, however, some advantage in relieving the irritation and pruritus associated with the migration of gravid female worms and the deposition of ova on the perianal region. They employ 2 per cent phenol ointment U. S. P. The employment of anal plugs and medicated jellies may be an aid in the control of the disease but as a rule cannot be depended on to eradicate infestation. They state that there is still a need for a cheap effective anthelmintic which can be administered with safety to persons of all ages and which can be employed with a minimum of effort.

The effects of single doses of tetrachlorethylene in the treatment of pinworm infestation have been observed by W. H. Wright, J. Bozicevich and L. S. Gordon.²⁸² The drug was administered orally at the rate of 0.1 cc. of each year of apparent age. It was

given in a solution of magnesium citrate. Of 44 infested children who received tetrachlorethylene orally and who were checked by posttreatment swab examinations on approximately the fourteenth and twenty-first days after treatment, 30 (68.2 per cent) were negative. However, the authors believe that the true percentage of cures was probably about 47 per cent since the former figure should be reduced approximately 30 per cent to account for positive cases not disclosed by 2 swab examinations. Three children received magnesium citrate solution alone, followed the next morning by an enema consisting of 1 cc. of tetrachlorethylene in a coconut oil soap emulsion to 1 liter of water. These 3 children were negative on posttreatment swab examinations, but in no instance did the magnesium citrate solution remove all the worms. So far as there is available evidence, it would appear that tetrachlorethylene is one of the best drugs for a single-dose treatment for pinworms. It is especially effective for light

pinworm infestations but would probably fail to effect cures in the majority of persons heavily infested, a failure which would probably be shared by other anthelmintics of merit when similarly administered.

Trichiniasis

The effect of sulfanilamide on the course of experimental trichiniasis in rats has been studied by O. R. McCoy.²⁸³ No differences were noted between the total number of larvae which developed in the muscles in the treated rats or of the control animals. Nor was there any evidence of any lethal effect upon the adult worms in the intestine or on the development of the larvae in the muscles. As judged by loss of weight during the course of the infection, the drug had no effect on the severity of the symptoms. Actually the treated rats lost considerably more weight than the control animals and also more than other rats which were given the same amount of the drug but were not infected with trichiniasis.

POISONING IN CHILDREN

WALDO E. NELSON, M.D.

Lead

An instance of chronic lead poisoning associated with active rickets in a child 3½ years of age is reported by J. Caffey.²⁸⁴ Evidences of lead lines in the bones were absent from the early roentgenograms, but appeared coincidentally with the healing of the rickets. The absence of lead lines in the skeleton during active rickets is explained by the close parallelism in the deposition of calcium phosphate and that of lead phosphate in growing cartilage. It is suggested that the skeletal lesions of lead do not develop during active rickets because the skeletal

changes in lead poisoning and in active rickets are antagonistic both physiologically and anatomically.

In an excellent article in which the pathologic lesions of lead encephalitis in children are described in detail, S. S. Blackman, Jr.²⁸⁵ states that patients who recover after the initial convulsions may be expected to have functional disorders varying from mental retardation to spastic paralysis. Clinically, fever and marked leukocytosis were present in most of the cases in this series and the signs of encephalitis appeared during the hot months of summer and fall in 19 of

the 22 cases. In another patient, dying in January, the encephalitis appeared in association with widespread lobular pneumonia. Blackman suggests that factors which cause vasodilatation, such as fever and the high temperature of summer weather, may be important in precipitating the lesions in the brain.

Naphtha

Acute naphtha poisoning in an infant, which they believe to be the first recorded, is reported by J. P. Price and F. Harrison.²⁸⁶ The infant swallowed liquid floor polish and almost immediately began to cough vigorously. Within a very few minutes he became extremely cyanotic, his breathing was slow, shallow and associated with a sonorous sound. The pulse was weak and rapid. The throat was somewhat red, but there was no evidence of any severe burning. *Caffeine sodium benzoate* was given as a stimulant and *gastric lavage* performed. Following the lavage, $\frac{1}{2}$ ounce of *magnesium sulfate* was left in the stomach. During the next 24 hours, the child had several periods of extreme restlessness, which were controlled with *chloral hydrate* administered rectally. By the following morning the child appeared to be in good condition. The cyanosis had disappeared, the pulse was of good quality and the boy was in excellent spirits. A few, scattered, moist rales appeared over both lungs.

It was believed that naphtha was the offending substance in the floor polish. The symptoms which result from the ingestion of naphtha are dependent upon the amount of poison swallowed and absorbed. The earliest symptoms are those caused by local irritation of the alimentary tract, a burning sensation in the mouth, throat and stomach, vomiting, thirst, and colicky pains. As the volatile products of the hydrocarbon are ab-

sorbed from the stomach, further symptoms arise; shallow respiration, weak pulse, cyanosis, extreme restlessness, and unconsciousness. The symptoms which result from aspiration of the poison are those of irritation of the respiratory tract; cough, tracheitis, dysphonia, bronchitis, and in severe cases bronchopneumonia.

Phosphorus

An instance of acute phosphorous poisoning with recovery in an infant who had eaten roach paste is reported by S. Blumenthal and A. Lesser.²⁸⁷ Particular emphasis was placed on the value of *continuous intravenous administration of dextrose solution*. Since the liver is unable to store sufficient amounts of glycogen, it becomes important to supply dextrose slowly and constantly to the blood stream until the liver can again take over its normal function.

Poison Ivy

Failure to obtain either prophylactic or therapeutic results with a standard poison ivy extract in oil is reported by L. C. Bachmann.²⁸⁸ Of 14 children who received 2 injections of 1 cc. each of the extract, as well as 7 children who received 3 injections, none was noted to have gained any more protection than the untreated children with whom they were associated. No therapeutic results were seen either immediately or late. There was no unusual relief from itching or from other symptoms, nor was there a definitely shortened course of illness.

Potassium Chlorate

An instance of a severe toxic encephalopathy which followed symptoms of acute poisoning in a child who had received potassium chlorate by mouth and 2 injections of sulfarsphenamine in the treatment of Vincent's stomatitis is reported by J. Greengard.²⁸⁹ While the

causal relationship of the encephalopathy to these drugs was not proved, it was considered likely. The author states that potassium chlorate should never be ad-

ministered internally to a child and doubts the justification for its local use, since there are other more efficient and innocuous oxidizing agents.

POLIOMYELITIS (Infantile Paralysis)

ROBERT A. LYON, M.D.

Several large *epidemics* of poliomyelitis have occurred in the United States during the past few years. One of the largest series of patients was reported from New York City by A. E. Fischer and M. Stillerman.²⁹⁰ From the survey of 686 hospitalized patients the authors summarized certain interesting features. There was a larger percentage of older patients in the group than in previous epidemics and these individuals developed paralysis less frequently than those of younger ages. Of the series of patients who entered the hospital in preparalytic stages, only 20 per cent developed paralysis. The total mortality rate (26 per cent) of the group studied was very low in comparison with that of previous epidemics and the rate for the city as a whole. In 17 families there were 2 or more cases, a total of 36 patients in all, while all of the other patients were the only ones affected in their families.

Fever seemed to be the best single criterion of activity of the disease and a high percentage of those with more than 500 cells in their cerebrospinal fluids developed paralysis. One-half of the 10 patients who had had their tonsils and adenoids removed within a month before the onset of poliomyelitis symptoms developed bulbar or encephalitic manifestations, which was a much higher percentage than occurred in the total series.

Schick tests performed on all of the patients showed a high incidence of posi-

tive reactions even among some persons who had received the preventive inoculations previously. This finding, which has been recorded by other authors, has suggested the possibility of a temporary loss of immunity of all types during the course of poliomyelitis. The treatment of the disease in this series of patients was mostly symptomatic without the use of convalescent blood or other sera. The Drinker respirator was found very efficacious in the treatment of patients with respiratory difficulty which occurred in 18 instances.

Diagnosis—*Cerebellar types* of poliomyelitis present many difficulties of diagnosis. E. Glanzmann²⁹¹ has outlined the symptoms of this form of the disease. Paralysis rarely occurs and the tendon reflexes vary considerably. They may be abolished or exaggerated, and occasionally they differ in intensity on the 2 sides of the body. Weakness of the legs and fatigue are common symptoms, but the diagnosis rests upon the presence of ataxia with a tendency for the child to fall to one side or the other. The finger-nose test and the heel-knee test are often performed with difficulty. Romberg's sign may be present, but it is often absent as is the rigidity of the neck. The tone of the muscles of the extremities may be weak without a definite paralysis. The cutaneous reflexes are frequently exaggerated. The cerebrospinal fluid is under little or no increase of pressure, is clear, and the Pandy

reaction is positive. It is always doubtful whether the cerebellar types are due to the poliomyelitis virus except when the symptoms occur during an epidemic of the more typical forms of disease. The prognosis of cerebellar poliomyelitis is usually very good.

The diagnosis of *nonparalytic poliomyelitis* also depends considerably upon the presence of an epidemic of the typical forms of disease. The symptoms of such patients may resemble those of other infections of the central nervous system, such as aseptic choriomeningitis and encephalitis. M. Brodie²⁹² investigated the sera of 24 patients who had had attacks of nonparalytic poliomyelitis 2 to 8 months previously, to see whether any antibodies against the virus of aseptic choriomeningitis were present. In no instance did the sera of these patients neutralize this virus. Another group of 17 patients who had had nonparalytic poliomyelitis were tested with the virus of the St. Louis encephalitis epidemic and their sera also produced negative results.

Attention has been called by R. DeMattia²⁹³ to the *early symptoms and signs* of poliomyelitis. He stressed the importance of the sharp pain which occurred very early in the disease at the junction of the muscle fibers and tendons. In the skin overlying the involved muscles there is a hyperesthesia and a diminution in the reflexes. Meningismus and hypotonicity of the muscles of the neck are other early signs of the disease which warrant an early diagnostic lumbar puncture and the careful examination of the cerebrospinal fluid for its cellular, sugar and albumin content.

Difficulty has been encountered in *isolating the poliomyelitis virus* from the nasal secretions of patients with the disease. M. Stillerman and M. Brodie²⁹⁴ were able to find only 11 reports in the medical literature in which the virus

isolated was definitely identified as that of poliomyelitis. They have added 1 more case to this group. In a series of 15 patients from whom weekly specimens were obtained, the virus was isolated in 1 instance from a girl 9 years of age, who was in the ninth day of her illness at the time when the virus was detected.

Attacks of poliomyelitis do not always confer permanent immunity. A. E. Fischer and M. Stillerman²⁹⁵ have reported 4 instances of *second attacks* of the disease, observed in New York City. Thirteen other cases of this type have been reported previously in the medical literature. A summary of these and other unpublished or doubtful instances has been compiled to bring the total number to 26 and intervals of 2 to 25 years between infections have been noted. In 1 of the authors' patients, no neutralizing substances for an F₁ strain of poliomyelitis virus could be demonstrated in the blood serum immediately after the second attack or 1 year later.

Treatment—The treatment of poliomyelitis patients with *intravenous hypotonic saline solution* has been recommended by G. M. Retan.²⁹⁶ A 0.375 per cent solution of sodium chloride was administered slowly for 3 periods of about 5 hours each. From 1500 to about 5000 cc. were given in this manner. Ten patients with respiratory paralysis and 6 with involvement of the muscles of deglutition responded favorably. It was believed that the respirator would not have been necessary in any of the former groups if the intravenous treatment could have been given as planned. A series of 16 preparalytic patients responded well with an improvement in muscle tone and the return of reflex action. This form of therapy has prevented paralysis and death in rhesus monkeys which had been injected with lethal doses of the virus. Patients who have paralysis of muscles of

the extremities do not improve. However, while the disease is active or spreading, as in the Landry ascending forms, considerable benefit might be expected from hypotonic saline therapy.

The *results of muscle treatment* of 36 patients during their periods of recovery from poliomyelitis have been reviewed by N. M. Harry.²⁹⁷ Treatment consisted of *complete rest* for the patient during the acute stage of the infection with the help of *plaster casts*. When muscle tenderness had disappeared, *radiant heat*, *massage* and *passive motion* were instituted. *Light exercise*, often with the muscle submerged in warm water, was then employed and in a few cases the weak muscles received *electrical stimulation*. The ages of the patients ranged from 4 to 14 years. The most rapid improvement occurred during the first 6 months after the acute manifestations of the disease and further progress was made during the next 4 months, but after a period of a year the changes were very slight. Sometimes the younger children, who co-operated less well at the start, continued to improve over a longer period of time. The time at which ambulatory treatment was begun depended a great deal upon the muscle groups involved. Paralysis of leg muscles usually required bed rest for about 1 year until no more improvement in function occurred, and then supports and braces were applied. When the spine and abdominal muscles were affected, bed rest often had to be prolonged for a longer period of time to prevent scoliosis, to allow readjustment of active muscle power and to permit growth to proceed as far as possible. It seemed impracticable, however, to keep any patient in bed over too long a period of time and, in many such cases, braces had to be provided to furnish the patients the maximum support when they got up.

The *treatment of the paralyzed muscles* has been divided into 3 stages, according to the plan of Lovett, by F. R. Ober.²⁹⁸ The first stage of acute symptoms with pain in the affected parts must be treated conservatively by *prevention of abnormal positions and contractions* with the aid of *padded splints*, *hot packs* and *sedatives*. The second stage of convalescence necessitates further efforts to prevent muscle contractions and marks the time for beginning *massage*, *baking*, and *passive and active exercises*. An accurate determination of the muscles affected is very essential so that strong muscles are not exercised at the expense of the weak ones. Complete rest is necessary during this stage and no attempts should be made to encourage early walking. During the third stage, which begins about 2 years after the onset of the illness and after the maximum recovery is to be expected, *operative procedures* and *re-education* measures may be started. *Electrical therapy* has seemed to this author to be of little value in the treatment of the paralysis of poliomyelitis.

Considerable attention has been paid recently to the rôle of *vitamin C* in the *resistance of a patient* to disease. The relationship of this vitamin to poliomyelitis has been investigated by C. W. Jungeblut.²⁹⁹ A series of 282 rhesus monkeys were infected intracerebrally with poliomyelitis virus and given vitamin C injections during the course of the incubation period. Compared with a control group of animals which received no vitamin therapy, the treated group escaped paralysis in a much higher percentage of cases. Natural vitamin C was much more effective in reducing the severity of the infection than was synthetic vitamin. Doses of 5 to 25 mg. given during the first few days of the incubation period seemed adequate, but

50 to 100 mg were required when the treatment was postponed until a few days before symptoms occurred.

The experiments have been continued by C. W. Jungeblut and R. R. Feiner³⁰⁰ by investigation of the vitamin C content of tissues. Animals that received vitamin C injections were able to store amounts which were greater than those found in normal control animals. The liver, kidney and intestines seemed to be the chief places of storage and some was also found in the spleen and brain but very little was stored in the spinal cord. Animals paralyzed by poliomyelitis virus had slightly lower levels of vitamin C in the nervous tissue and suprarenals than the average figures. The tissue of animals which had received vitamin C injections and had become paralyzed had levels of the vitamin quite comparable to those of control groups but the animals which had escaped paralysis had higher levels than average.

Prevention- *Nasal sprays* will not cover the entire surface of the mucous membranes of the nose unless special technic is employed. A full description of this procedure has been given by R. S. Pentecost.³⁰¹ Important features are the placing of the patient in a recumbent position with the head retracted, preparing the mucous membranes with a preliminary spray of a pontocaine and ephedrine mixture and then injecting 0.5 cc of the zinc sulfate solution with a special catheter inserted between the middle turbinate and the nasal septum. After 1 minute the patient is instructed to sit up and snuff the solution up the nose and expel it through the mouth. Loss of ability to smell occurred in all patients for a period of about 5 days and headache for 2 to 6 hours was a universal complaint.

The application of chemical agents to the nasal mucous membranes has been

made by L. Shahinian, J. A. Bacher, R. C. McNaught and R. R. Newell³⁰² by means of a nose dropper without any previous shrinking of the nasal tissues. The most important factor in such therapy, in their experience, was the placement of the patient in a recumbent position with the head tilted backwards so that the base line of the skull was horizontal.

Blockage of the nasal area with zinc sulfate solutions will prevent the entrance of the virus of poliomyelitis by that route but does not prevent the infection from being introduced intravenously. J. A. Toomey and W. S. Takacs³⁰³ have demonstrated this point with experiments in rhesus monkeys. This would indicate that the virus, introduced into the blood stream, is secreted in places other than nasal mucous membranes.

Immunity to poliomyelitis has been produced in monkeys by the intranasal instillation of *pituitrin S* and *adrephepine*. S. D. Kramer, L. H. Grossman and G. C. Parker³⁰⁴ used such instillations twice a day. When the virus was instilled 12 to 24 hours later, two-thirds of the group of animals survived and there seemed to be evidence of the development of an active immunity. A large percentage of another group of animals which received combined pituitrin S, adrephepine and virus instillations daily also survived infection. Subcutaneous injection of the 2 chemicals produced no protection. Although the nature of the action of these nasal instillations was not determined, it seemed likely that this might be a method of producing a protection against poliomyelitis and might lead to an active immunity against the disease.

Recent experiments have shown the poliomyelitis virus is extremely sensitive, *in vitro*, to *ultraviolet irradiation*. C. W. Jungeblut³⁰⁵ found that exposure from

1 to 30 minutes killed the virus. It was considered possible that oxidation was a factor involved in this process.

Methylene blue solutions of 1:50,000 to 1:100,000 concentration have been

found by L. A. Rosenblum, B. Hoskwith and S. D. Kramer³⁰⁶ to inactivate poliomyelitis virus when exposed to the light of a 100-watt bulb for about 60 minutes.

RESPIRATORY SYSTEM

By WALDO E. NELSON, M.D.

Asthma

In contrast with those who have reported clinical improvement in persons with bronchial asthma after the administration of ascorbic acid, H. B. Hunt³⁰⁷ has not found ascorbic acid to be of any value in the treatment of bronchial asthma when given in comparatively large doses either by injection or by mouth

Colds

Prevention—A study has been carried out by M. H. McKee³⁰⁸ to determine whether the incidence of upper respiratory infections could be reduced by the employment of tannic acid nasal sprays. No differences in the incidence of upper respiratory infections nor in the recurrence of rheumatic infections were observed between the treated and control groups

Empyema

Tidal drainage in the treatment of acute uncomplicated empyema in children has, according to A. Weller,³⁰⁹ definite advantages over both the older methods of closed drainage and of rib resection. The author employed the method of Overholt and states that it is an improvement over the older method of closed drainage in which the drainage bottle was placed too far below the level of the fluid in the chest. This often resulted either in occlusion of the tube by large clumps of fibrin or by the mobile lung. Tidal drainage regulates the level

of fluid inside and outside the chest. The drainage bottle is placed on a table so that the level of fluid in the bottle is only between 2 and 4 inches below that in the chest. The resulting syphonage pressure is less than the intrapleural pressure and a slight to and fro movement is set up



Fig. 19—The catheter in place. The adhesive has been removed to show the position of the mushroom catheter, flush with the chest wall. (J. Pediatr. Jan., 1938.)

within the system with each respiration. Thus the tube is continuously washed out and large clumps of fibrin are broken up. In addition the lung expands slowly, giving the empyema cavity time to become sterilized and emptied.

The method is as follows. The skin is prepared with green soap and alcohol and the interspace to be used is infiltrated with a small amount of novocaine. The site of choice is in the axilla, sufficiently

high to avoid the diaphragm and far enough forward so that the movements of the scapula will not interfere with the tube. The fifth interspace in the mid-axillary line is used in infants and the sixth interspace in older children. Morphine sulfate is given $\frac{1}{2}$ hour before the procedure is started. A skin incision of about 3 or 4 mm. is then made and a

then withdrawn, leaving the catheter in place. It is important to keep the catheter clamped off until it is connected to the drainage system. A number 32 mushroom catheter, which has been modified by cutting out the center of the mushroom and using about 2 inches of the length, is then lubricated and slid over the plain catheter until the flanged por-

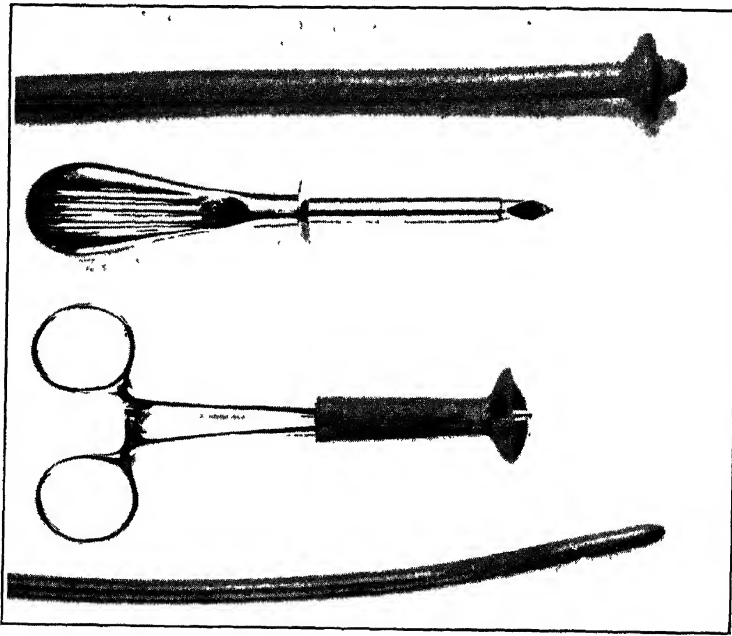


Fig. 20—The instruments used. From above downward: a No. 32 mushroom catheter, a trocar and cannula, the modified end of the mushroom catheter with snap inserted, and a No. 20 French rubber catheter. (J. Pediat., Jan., 1938.)

trocar and cannula are inserted into the chest. The cannula should hold a No. 20 French rubber catheter snugly. The catheter should have an extra hole about $\frac{3}{4}$ inch from the tip on the side opposite the one already present. The other end of the catheter is cut off so that about 10 inches of the tube remains. The exact length of the catheter should be known so that the amount in the chest can be readily determined. To prevent air from entering the chest, the catheter is inserted through the cannula as soon as the trocar is withdrawn and about 4 inches of the catheter is introduced. The cannula is

then withdrawn, leaving the catheter in place. It is important to keep the catheter clamped off until it is connected to the drainage system. The mushroom catheter is then secured to the chest wall by means of adhesive straps in order to keep the system air tight. The skin should be painted with tincture of benzoin before applying the adhesive.

The drainage system consists of a regular infusion jar to which is attached a rubber tube, a drip bulb without a side opening, which in turn is attached to another rubber tube, the other end of which is attached to a glass "Y". The other two arms of the glass "Y" tube are connected to the catheter from the

chest and to the drainage bottle respectively (see Fig ??).

The drainage bottle is placed on a table so that the level of fluid is about 4 inches below that in the chest. In this way tidal drainage is established and the fluid in the glass adapter and "Y" tube

away from the chest aids in dislodging them. As the cavity is drained, the catheter may be gradually shortened. This is done by holding the mushroom firmly in place and slowly pulling the catheter until eventually only $1\frac{1}{2}$ to 2 inches remain in the chest. As the size

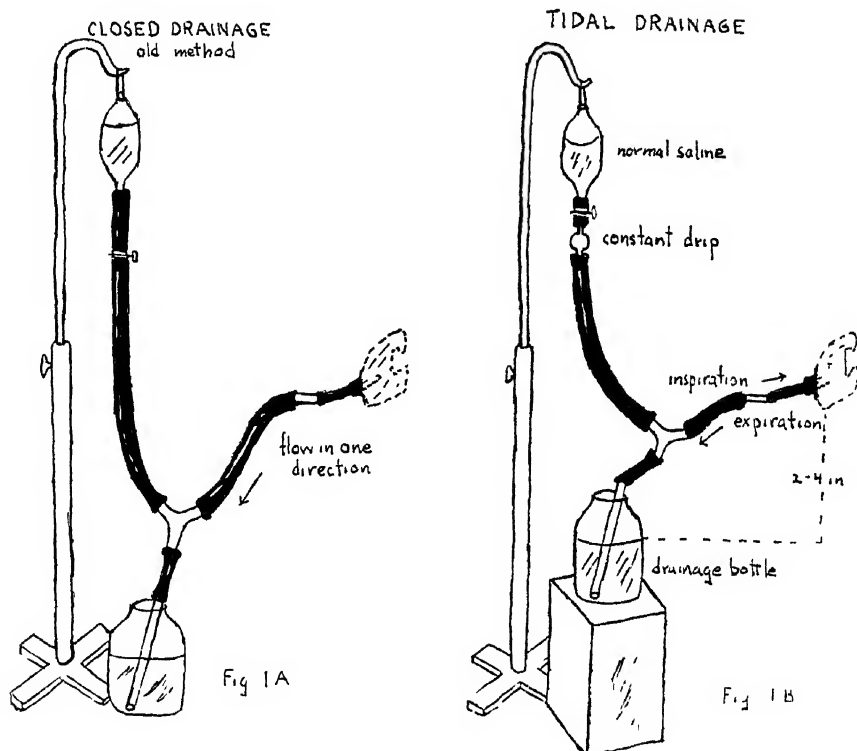


Fig 21—A represents the usual method of closed drainage. The drain bottle is on the floor, producing excessive siphonage pressure. Fluid flows in one direction except when the chest is irrigated. Occlusion of the tube frequently occurs. B represents tidal drainage. The fluid in the drainage bottle is two to four inches below that in the chest so that on inspiration the siphonage pressure is overcome. The to-and-fro movement prevents plugging of the catheter. (J. Pediat., Jan., 1938.)

will be seen to oscillate with respiration. In addition to the tidal drainage which occurs with respiration, the chest is irrigated every few hours for several days until there is thinning of the pus. This is accomplished by clamping off the tube leading to the drainage bottle and allowing 25 or 50 cc. of saline to flow rapidly into the chest. If large clumps of fibrin should occlude the tube, pinching the rubber and milking it both toward and

of the cavity diminishes, irrigation may force pus out along the side of the catheter. Although fluid may escape in this way, the flange portion of the mushroom will prevent air from entering the chest.

Foreign Body

According to M. F. Arbuckle¹⁰ non-opaque foreign bodies are aspirated relatively frequently. They are of many different sorts and may include any ob-

ject which may be placed in the mouth and which is small enough to pass through the larynx. In making the differential diagnosis, the history is one of the most important steps. Any positive point in the history should not be disregarded. It happens in some instances that such patients are seen during what has been described as the symptomless interval. The presence of any accompanying disorder such as an upper

grams of the chest, both during inhalation and exhalation. On fluoroscopic examination, the movements of the chest wall and the diaphragm on the 2 sides and any change in position of the heart during the respiratory cycle should be noted. These movements should be studied carefully during inhalation and exhalation. The roentgenograms should be made in pairs on a fast machine, one at the end of full inhalation and one at

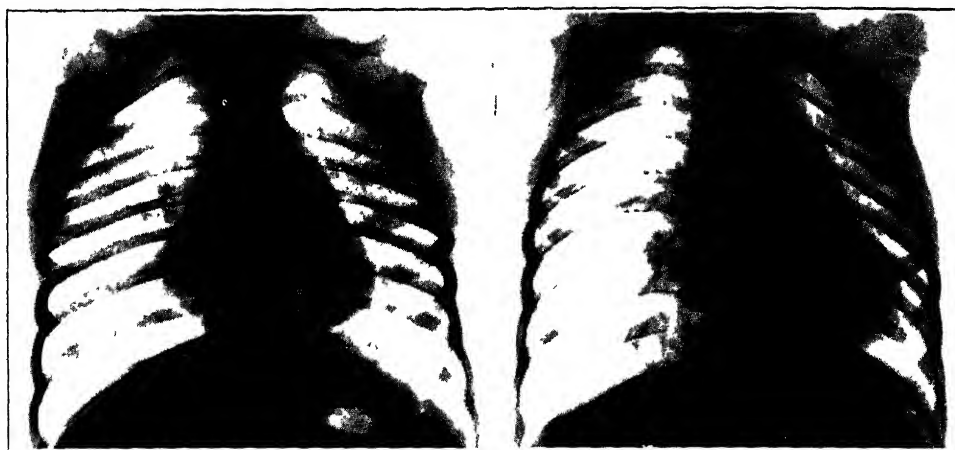


Fig. 22—At bronchoscopy a fairly large portion of a peanut was removed from the right main bronchus. (J. Pediat., Sept., 1937.)

respiratory infection should not be permitted to overshadow the importance of the positive history of foreign body. The special signs which are pathognomonic of the presence of foreign body in the tracheobronchial tree are: The "asthmatoïd wheeze," the "audible slap," the "palpatory thud," the "audible flutter," and the "split cough." These are of especial importance when associated with a history of sudden attack of choking, coughing, cyanosis or dyspnea. It is pointed out by the author that both lungs are usually involved, the unobstructed lung by the overflow of mucus and pus and as a result of the compensatory function.

The examination should also include fluoroscopic observations and roentgeno-

grams of the chest, both during inhalation and exhalation. It is stated that cardiac shift and the movements of the diaphragm on the unobstructed side depend upon inflation and deflation of the unobstructed lung. In unilateral obstructive emphysema, it will be noted that the diaphragm on the obstructed side is pushed down and remains in a more or less fixed position and that while the diaphragm on the unobstructed side moves freely with respiration, the heart is shifted to the unobstructed side at the end of exhalation, and pushed back to its normal position during inhalation (see Figs. 22 and 23). The ribs on the unobstructed side occupy the horizontal position at the end of full inhalation and drop to the more vertical position at the end of full exhalation.



Thirty minutes before removal of peanut from right main bronchus
 Thirty minutes after removal
 Twenty-four hours later
 Fig. 23 (Case 6)—Atelectasis of the right lung with cardiac shift (J. Pediat., Sept., 1937)



Inhalation
 Exhalation
 Inhalation
 Fig. 24 (Case 7)—Atelectasis of the lower lobe and obstructive emphysema of the upper lobe (J. Pediat., Sept., 1937)

There is also greater width in the intercostal spaces at the end of inhalation, *i. e.*, full inflation of the lungs. The ribs on the obstructed side remain in a more horizontal position with widened intercostal spaces.

In bilateral obstructive emphysema caused by partial tracheal obstruction, there is increased air content in both lungs throughout the respiratory cycle, with increased intrapulmonary pressure on both sides. This increase in pressure is demonstrated by the depression of the dome of the diaphragm on both sides, the elevated position of the ribs, and the change in the size and shape of the cardiac shadow as a result of compression of the heart and mediastinum from both sides.

In atelectasis, the heart is shifted toward the area of collapsed lung and fixed in this position, the diaphragm on the obstructed side is elevated and fixed, and the ribs are in the vertical position (see Fig 24, Film 1).

In the presence of combined atelectasis and obstructive emphysema the findings partake of both of these conditions (see Fig 24). In this instance, with atelectasis of the left lower lobe and obstructive emphysema of the left upper lobe, the diaphragm on the obstructed side was elevated and the apex of the heart shifted toward the area of atelectasis, while the base of the heart was shifted away from the area of obstructive emphysema. The upper ribs were in the horizontal and the lower ribs were in the vertical position.

Roentgenographic diagnosis of unimpacted foreign body depends upon the ability to visualize fluoroscopically the changes as they occur and to secure films during the short interval in which the foreign body remains stationary. When there is doubt regarding the diagnosis in cases which have positive his-

tories or in which any of the above findings are positive, even in the presence of a negative history, bronchoscopy should be recommended.

Grippe

An interesting report on clinical observations of so-called grippe as seen in pediatric practice is made by C. A. Aldrich.³¹¹ The study is based on 1146 cases which occurred in 845 different children between February, 1930, and January, 1936. There were 222 second attacks in the same children, 58 third attacks, 15 fourth attacks, 5 fifth attacks, and 1 sixth attack.

The author divides the symptoms into 3 groups: Those present at the onset, those occurring in the first 3 days, and those developing later. They are as follows:

A. Symptoms and Observations at the Onset:

1. Chill or chilly sensation (this may have to be demonstrated by direct questions)
2. Sudden fever
3. Red conjunctivae
4. Normal nasal and pharyngeal membranes
5. Relatively slow pulse
6. Toxic symptoms, frontal headache, prostration, malaise, vomiting, anorexia, flushed face (cyanosis rarely seen in children), muscular aches in older children only
7. Leukopenia

B. Symptoms and Observations During First 3 Days

1. A fluctuating fever
2. Reddening of nasal and pharyngeal membranes
3. Cough--laryngeal in type
4. Relatively slow pulse
5. Coated tongue--often thickly furled, with sharply demarcated red rim
6. Signs or symptoms of complications, usually in the ears or chest
7. Modification of the blood count with purulent complications

C. Observations Made on the General Course of the Disease:

1. Rapid recovery after a few hours, or

- 2 Prolongation for several days or weeks without demonstrable complications, or
- 3 Prolongation due to evident complications,
- 4 Improvement, usually associated with a mucous discharge from nose, throat, and bronchi, and with progressive clearing of tongue
- 5 Tendency to relapse, following apparent recovery

During the period of observation, grippe occurred in yearly epidemics of considerable proportions except in the winter of 1933-34, when there was an obvious but smaller wave. Laryngitis and croup occurred in smaller epidemics identical in time with those of grippe, making it appear probable that croup is a manifestation of grippe in infancy. On the other hand, the epidemics of grippe showed no chronological relation to the prevalence of general respiratory disease as shown by comparison with the incidence of pharyngitis. The most common complications were otitis media and capillary bronchitis. In the author's experience, capillary bronchitis occurred, with any degree of frequency, only in measles and grippe. Seventy per cent of the children who developed capillary bronchitis were known to be asthmatic, and another 17 per cent were probably allergic. Aldrich raises the question whether the physical findings responsible for the diagnosis of capillary bronchitis might not be due to an allergic reaction within the bronchi. The prognosis was extremely good. The only death was from meningitis, which resulted when measles complicated grippe with mastoiditis.

Laryngitis

In the experience of W. A. Howard⁵⁷ intubation rather than tracheotomy is the procedure of choice in the management of the acute stage of both diphtheritic and nondiphtheritic laryngeal

obstruction. He states that tracheotomy performed during the acute inflammatory stage is apt to result fatally, whereas when done on specific indications after the acute stage is passed it is almost uniformly successful. In contrast to those who believe that intubation tubes are apt to cause damage to the larynx, the author reports instances without laryngeal damage even when the tube was left in place for as long as 14 days. The prognosis of acute obstructive laryngitis in children appears to be chiefly influenced by the duration of the obstruction rather than the duration of the disease.

Otitis Media

Beneficial results from the employment of *urea* in chronic otitis media are reported by P. S. Mertins, Jr.³¹² The work of the author was stimulated by that of Holder and MacKay, who employed urea solution in the treatment of chronically infected wounds. They believed that while the urea might have some bactericidal effect, its action was chiefly through the solvent action on proteins, resulting in the removal of debris, incrustations and dead tissue, which deter normal healing by harboring bacteria. The author employs a saturated solution of urea which is injected twice daily with a dropper, beginning with small amounts and increasing rapidly if there is no pain. The crystals may also be applied directly or with a powder blower. Care should be taken to remedy any caking either in the canal or in the powder blower. A small amount of water or saline solution is usually corrective. Urea should be used cautiously, if at all, in the presence of cholesteatomata and should not replace surgery when indicated. The crystals, while less satisfactory than the solution, are entirely safe in this condition.

Pneumonia

Good results from blood transfusions in primary pneumonia in infants and in children is reported by J. M. Arena.³¹³ The intravenous administration of any appreciable quantity of fluids in cases of pneumonia is usually considered a hazardous procedure since it increases the load of an already overtaxed heart. However, according to Arena, the severe dyspnea and cyanosis, which many of these children had, were improved instead of made worse by these transfusions. No circulatory embarrassment was noted after any of the transfusions. Several of the patients had an immediate rise in temperature after the transfusion, which was usually followed by an immediate crisis. The children were given 1 or more transfusions of citrated blood by the gravity method. The maximum amount was 20 cc per kg of body weight. The control group consisted of 35 children, who were not given transfusions. The average interval between the onset and the crisis was shorter and the mortality lower for the children who received transfusions than for those who did not. Prompt and marked symptomatic improvement usually followed the transfusion and the patient appeared more comfortable. Temperature fell by crisis within 24 hours of transfusion in 15 patients, within 48 hours in other 9.

No explanation for the beneficial effect of the blood transfusions is known.

The results were as good in patients with severe anemia as those with moderate anemia. Such explanations of the beneficial effect as the stimulation of segmented polymorphonuclear leukocytes, the introduction of neutralizing antibodies, or the supplying of more red cells to carry oxygen to the tissues are considered.

Ear Complications—The importance of watching for ear infections during the acute and convalescent stages of pneumonia in children is pointed out by C. E. Towson.³¹⁴ In a series of 354 cases of pneumonia in children, Towson observed aural complication in one-third of them. The incidence of aural disease was about equal in bronchopneumonia and in lobar pneumonia. Although otitis media associated with pneumonia is often symptomless, in this series there was, in most instances, an added elevation of temperature. When otitis media is followed by surgical mastoiditis, it usually develops between 2 and 4 weeks after the onset of otitis media. The roentgenogram cannot be relied upon to make the diagnosis of acute mastoiditis, since negative films do not preclude the possibility of mastoid involvement. In the author's series, the streptococcus was the common invading organism, and not the pneumococcus. In 2 instances, postmortem examination revealed mastoid disease without evidence of middle-ear involvement.

RUBELLA (German Measles)

By ROBERT A. LYON, M.D.

Six cases of *meningoencephalitis* following German measles have been reported recently by C. Davison and L. Friedfeld.³¹⁵ An autopsy was performed in a patient 22 years of age and in the

brain was evidence of slight meningeal irritation and perivascular infiltration of the white and gray matter of the cortical convolutions, the brachium pontis, and portions of the cerebellum and medulla.

The nerve cells of third, fourth and seventh cranial nerves were vacuolated, which may have been the result of high fever or toxemia.

The symptoms which usually appeared suddenly within 1 to 6 days after the fading of the rash consisted of headache, irritability, vomiting and signs of meningeal irritation. The pupils often reacted sluggishly to light, and strabismus, diplopia and nystagmus were encountered. In several instances the tendon reflexes were exaggerated, and paraplegia, sensory disturbances, cerebellar and extrapyramidal lesions were observed. The cerebrospinal fluid was generally clear and contained none to 100 cells, mostly lymphocytes. Otherwise the chemical and bacteriological examinations of the fluids were normal. The only treatment was that of relieving the symptoms, which included *drainage of the cerebrospinal canal*.

The *prognosis* of the reported patients is either rapid death or complete recovery. Until the year 1935, only 2 instances of central nervous complications of rubella had been reported but severe epidemics of the disease have oc-

curred since that time and more reports of it have been appearing.

The occurrence of *meningoencephalitis* following German measles in a white man aged 26 years was observed by C. F. Read³¹⁶. On the sixth or seventh day after the onset of symptoms of rubella, the patient developed thickness of speech, dizziness, projectile vomiting, and loss of equilibrium. Twitching of the fingers, a lateral nystagmus and stiffness of the neck were detected on physical examination and the cerebrospinal fluid was under increased pressure with a cell count of 4. Within the next 2 weeks a rapid and complete recovery took place. Reports of 17 other such patients were found in the medical literature. The ages of these patients ranged from 3 to 33 years and common symptoms were headache, convulsions, rigidity of the neck, mental confusion, disturbances of vision and unusual movements of the eyes. The complication seemed to develop on the second to seventh day after the appearance of the rash and the mortality rate of the entire group of 18 (including the 1 reported above) was 11.1 per cent.

SCARLET FEVER

By ROBERT A. LYON, M.D.

Epidemiology—In reviewing certain aspects of the incidence and mortality from scarlet fever, S. D. Collins³¹⁷ stated that the deaths from this disease averaged 86 per 100,000 population in Massachusetts between the years 1855 to 1874 and a downward trend has occurred in the years since. The average number of deaths for the 5-year period of 1930-34 was 2.5 per 100,000 population, with figures in some years as low as 1.8. The experience of Massachusetts

has been paralleled by other States and, since the incidence of the disease has remained about the same throughout these years, one might conclude that the virulence of the infecting organism has diminished.

The disease has tended to occur more frequently in children of preschool age in the southern states and the incidence was greater in older children in the northern states. During the 2 years of 1929 and 1930 a total of 356,855 cases

of scarlet fever were reported and 4858 deaths occurred in this group, a mortality rate of 1.98 per 100,000 population or 1.35 deaths in every 100 cases of the disease. Probably many instances of the disease were not reported, so that the reported case mortality rates may have been higher than was really the case. The majority of deaths occurred in children 1 to 3 years of age, with the peak at the age of 3 years. A fairly large number of deaths also occurred in the young adult years.

An epidemic of scarlet fever and tonsillitis resulting from infected milk has been reported by R. Watson.³¹⁸ The epidemic lasted 12 days and was traced to the milk of 1 dairy. A streptococcic mastitis was found in 1 cow and 1 of the milkers had had a sore throat the week previous. Pasteurization of the milk was required and the epidemic ceased. A total of 135 patients developed scarlet fever apparently from this source, and 229 additional persons had sore throats only. Children of preschool age and adults were affected in larger proportions than usual in ordinary outbreaks of scarlet fever. The patients treated at home seemed to do as well and to have no more complications than those sent to isolation hospitals.

Diagnosis — The importance of examination of throat cultures in patients with scarlet fever and related sore throats has been emphasized by W. R. F. Collins.³¹⁹ In testing the strains of streptococci obtained during epidemics of scarlet fever and pharyngitis, he observed that the occurrence of powerful toxigenic strains of organisms in the nose and throat cultures was associated with outbreaks of large numbers of cases of scarlet fever, but when the strains were capable of producing toxin of medium or low potency, only a few cases of true scarlet fever occurred but many milder

infections of the throat developed. In a school epidemic in which 2 boys developed scarlet fever and 4 others a pharyngitis, routine nose and throat cultures of the entire student body were made. Pure growths of streptococci were obtained from the 4 patients with sore throats and 4 more healthy carriers were detected. Other cases of pharyngitis developed until Dick tests were performed on all of the children and scarlet fever antiserum was administered to the positive reactors. The author urged that culture methods be adopted more widely to control epidemics, because there is no other way of detecting carriers and subclinical cases caused by the specific organisms which act as sources of spread of the infection.

Complications — The incidence of *otitis media and related complications* of scarlet fever has been reviewed by A. L. Hoyne and R. Spaeth.³²⁰ Among 3564 patients with scarlet fever, purulent otitis media developed in 13.35 per cent and catarrhal otitis media in an additional 0.8 per cent. Previous reports representing 134,862 patients with the disease have indicated an incidence of purulent otitis media varying between 7.6 and 23.0 per cent, with an average of 11 per cent. Approximately 45 per cent of a series of 476 cases of otitis media developed mastoid involvement and slightly more than half of the group required surgical treatment.

Mastoiditis occurred in 6 per cent of the total group of scarlet fever patients and other complications associated with the mastoid infection were, in order of frequency, septicemia, lateral sinus thrombosis, jugular bulb thrombosis, intracranial abscesses and endocarditis. A third of the cases of otitis media developed during the first week of illness and 95 per cent during the first 6 weeks. The complication was more frequent in

early years of life and seemed to be definitely related to high mortality rates. Since otitis media is one of the most important of all of the complications of scarlet fever, the author recommended that prophylactic measures of all kinds which would reduce the incidence and severity of the disease be carried out. Treatment of the nose to promote free breathing space was important but gargles seemed to be contraindicated. Paracentesis of the drum should be postponed as long as possible and repeated incisions avoided unless amply justified.

Arthritis has occurred in 0.95 per cent to 2.18 per cent of the scarlet fever patients observed at the Willard Parker Hospital during the past 4 years by C. S. Boyd.³²¹ This group did not include patients with joint pains following serum injections. The average incidence among 5549 patients was 1.78 per cent. The complication developed more frequently in older children than young ones, was more frequent in females and generally occurred on the fourth to tenth day of the disease. Treatment consisted of rest for the affected joints, local application of methyl salicylate and the administration of sodium salicylate or aspirin internally.

Acute cholecystitis occurred in 2 patients with scarlet fever observed by A. T. Swing and J. G. M. Bullowa.³²² Symptoms of abdominal infection occurred 2 days before the appearance of the scarlatinal rash in a boy 13 years of age, and on the twenty-first day of the scarlet fever in the second patient, a boy of 9 years of age. Icterus developed in the latter patient and recovery was complete without operation. Exploratory operation on the first child showed no evidence of infection but drainage from the upper part of the wound was considered to be evidence of gall bladder infection. Five other reports had oc-

curred in the medical literature of liver and gall bladder involvement associated with scarlet fever.

Meningeal irritation of various types occurred in 36 of a series of 17,311 consecutive scarlet fever patients, reviewed by F. H. Top and J. E. Gordon.³²³ In 5 of this group, other infections than scarlet fever were the cause of the complication. Tuberculous meningitis developed in 4 cases and meningococcic meningitis in 1 other. Of the 31 patients with a meningeal reaction attributed to scarlet fever alone, 20 had purulent leptomeningitis, 4 had a localized pachymeningitis, 2 had serous meningitis and 5 had meningismus.

Encephalitis of a toxic nature developed in 12 patients during the course of scarlet fever and an additional group of 11 contracted more severe forms of encephalitis during the period of convalescence from the disease. The latter patients had symptoms resembling epidemic encephalitis and some of these individuals had residual changes of personality and behavior.

Treatment—Sulfanilamide was found to be of little value in the treatment of scarlet fever patients by J. C. Hogarth.³²⁴ He divided the scarlet fever patients admitted to a hospital during the course of a year into 3 groups. One series of 114 patients received *sulfanilamide* and *scarlet fever antitoxin*, the second, a group of 126 patients, received scarlet fever antiserum alone, and the third group of 115 patients had no specific treatment. The dosage of the drug was 0.5 Gm. 3 times a day for 3 days, the same amount twice a day for the next 4 days. On the sixteenth day of the illness, 0.5 Gm. was given twice a day for 7 days. Children under 5 years of age received smaller amounts. The patients receiving sulfanilamide had no shorter periods of fever and no fewer compli-

cations than the other groups. Toxemia seemed to be less in the 2 groups receiving antiserum than in the control series, but no added benefits from sulfanilamide were noted.

Sulfanilamide was ineffective in eliminating the streptococci from the throats of scarlet fever carriers treated by A. L. Hoyne and J. H. Bailey.³²⁵ Prontylin was given in doses of 5 grains 3 times a day for 7-day periods. Later the dosage was doubled in an effort to obtain better results. A total number of 125 patients received this therapy and 36 (20.8 per cent) had negative cultures of their nose and throat secretions by the end of the quarantine period. Of a series of 58 untreated patients, only 7 (12 per cent) had negative cultures. The authors believed that their control series was too small to be of significance since previous studies had indicated percentages of 30 to 40 with negative cultures at the end of quarantine periods. They were reluctant to attribute any beneficial action of sulfanilamide in hastening the elimination of streptococcus from scarlet fever patients.

Human convalescent serum has been found superior to commercial antitoxin in the treatment of scarlet fever patients by M. J. Fox and M. Hardgrove.³²⁶ Comparisons were made of the results from the administration of scarlet fever antitoxin to 139 patients, human convalescent serum to 589 patients, and ordinary treatment without serum injections of 300 control subjects. The age and sex distribution in the groups was approximately the same and most of the patients were observed in hospital wards. The improvement of symptoms and the early return of temperatures to normal levels were greatest in the group receiving convalescent serum. Complications and mortality rates were also lower in the same group. Reactions to the treatment

occurred in 35 per cent of the patients receiving antitoxin and in only 1 per cent in those receiving convalescent serum (see Table).

Convalescent serum has been used with success in the prevention and treatment of scarlet fever by C. M. Hyland and L. R. Anderson.³²⁷ Of a group of 102 persons who were exposed to scarlet fever, serum was given in doses of 10 cc to children less than 10 years of age and 20 cc to children over that age. Only 4 persons developed the disease and their attacks were mild. To 3 of these 4 patients the injection had been given on the second day of exposure. In the fourth case the scarlet fever was moderately severe but the serum had not been administered until the fifth day of exposure. In every instance the period of incubation was prolonged and no complications developed. In another group of 47 patients with scarlet fever, the convalescent serum was administered on the first to tenth day after the onset of the illness. The doses for infants were 20 cc, for older children 20 to 40 cc, and for adults 40 to 60 cc. In 6 cases the response to the injection was striking and in the remaining 40 there was some improvement during the 12 to 24 hours after the injection. Only 1 individual seemed to derive no benefit from the serum. It seemed very important to give the treatment early in order to obtain the best results, since complications occurred in only 18 per cent of those receiving the treatment on the first day and in 60 per cent of those who were not treated until the fourth day. An important factor in the treatment of scarlet fever by this means is the administration of an adequate dosage. If the disease is severe, the serum may be given intravenously and intramuscularly, but in mild attacks it may be administered by the latter route only. When the serum is used for the prevention of the

THERAPEUTIC VALUE OF CONVALESCENT SERUM IN SCARLET FEVER

	Hospital Group			Home Group
	Control	Antitoxin	Convalescent Serum	Convalescent Serum
Number of Patients (total 1028)	300	139	295	294
Severe or Complicated Scarlet Fever	57%	100%	95%	39.8%
Patients Ill Less Than 5 Days Before Hospitalization	83%	99%	87%	Less than 3 days, 79.3%
Average Time Until Normal Temperature Was Reached After Admission to Hospital	10.9 days	15.3 days	9.2 days	From onset of illness, 4.25 days
Average Time Until Normal Temperature Was Reached After Treatment		12.8 days	4.58 days	1.66 days
Average 12 Hour Drop in Temperature		2.1° F	3.5° F	3.4° F
Satisfactory Response		60%	90%	First 3 days, 68.4%; after 3 days, 14.9%; total, 83.3%
Complications Following Treatment		35%	16%	12.9%
Reactions		35%	1%	1%
Deaths	6 (2%)	4 (2.8%)	8 (2.7%)	5 (1.7%)

(M. J. Fox and M. Hardgrove, Arch. Int. Med. 60:494 (Sept.) 1937.)

disease it is necessary to remember that the immunity lasts for only 10 days to 2 weeks, and the therapy must be repeated if there is further exposure. The authors have also employed this treatment in 22 patients with other types of streptococcic infections. Although it was usually administered late in the disease, the serum seemed to be distinctly beneficial for 8 of the 14 patients who survived.

Purified scarlet fever antitoxin with a low protein content has been found to give less severe reactions than the unmodified products in the experience of J. A. Toomey and C. S. Baker.³²⁸ Three commercial products of the purified and concentrated antitoxin were employed. The first product was given to 800 patients, the second to 92 and the third to 30. Serum reactions of the first group were most frequent in patients 5 to 20 years of age, and the benefits derived from the serum were greatest in

those who had no or slight reactions. The effectiveness of the therapy in regard to the reduction of incidence of complications seemed to be as good or better than in previous years when unpurified antitoxin was used, but, in the absence of control patients, the authors considered the possibility that the general severity of the disease might have declined during the same period of time. Their experience with the second and third type of antitoxin products was more limited, but they concluded that reactions resulting from the purified products were materially less than from the regular untreated material.

Immunization—Successful results from the immunization of nurses have been reported by E. H. Place.³²⁹ In a period of years between 1913 and 1924, before immunization methods were available, scarlet fever developed in 8.6 per cent of the 1009 nurses who came in

contact with the disease in a contagious disease hospital. Since then, the protective injections of toxin have been given to 1446 nurses and the incidence rate has been 1.4 per cent. Of the group of 20 nurses who contracted the illness, 13 had not been immunized, 3 had had insufficient amounts of antigen, 1 had received a modified toxin and only 3 could be said to have received an adequate amount of immunization. The degree of contact with scarlet fever was a little less in the case of the nurses of the past few years, but the differences seemed to be insignificant. There was no indication that any general decreases in prevalence of the disease occurred in the same period of time and the nursing group did not appear to be contracting unrecognized forms of the infection.

Immunization of large groups of men in the army of Finland has been successful in reducing the incidence of scarlet fever. J. Wickström³³⁰ found that approximately 12 per cent of a series of 3367 soldiers had positive Dick reactions. About 20 per cent of Dick positive reactors contracted the disease in contrast to 0.34 per cent of those with negative Dick reactions. Immunization with formalin-treated toxin and with raw toxin caused a reversal of skin reaction in 70 to 100 per cent of the groups treated. Reactions with the latter material were more severe, so that the formalized toxoid was used most frequently in a mass immunization campaign. Scarlet fever developed subsequently in 4 per cent of the immunized and in 14.4 per cent of those who had not been treated. It was suggested that any immunization campaign should be carried out with material made from streptococci of local origin since that strain might be most efficient in combating the local disease.

Some of the severe reactions following the injection of scarlet fever toxin for

immunization purposes were avoided in a series of children treated by C. A. Stewart and E. S. Platou³³¹ by diluting the material to one-half of its original strength and then by dividing the dosage into 10 semiweekly or weekly injections. A group of 526 children immunized in this manner was observed for an average period of 31 months and during that time only 4 children contracted scarlet fever, all of the cases being of a mild character.

Such severe local or general reactions frequently result from the immunization of patients against scarlet fever that other methods of administration of the antigen have been sought. R. A. Kern, J. Crump, R. L. Roddy and S. Borow³³² have employed *intracutaneous injections of the toxin* with considerable success. The initial dosage was 25 to 50 skin test units and this was built up at weekly intervals to as high as 2500 to 4500 units. Dick tests were first performed 6 days after the third injection and subsequent tests made after successive doses until negative results were obtained. Of a series of 140 susceptible children, 129 became negative. Of 117 who had 4 doses or more, 106 (90.6 per cent) became negative, most of them after 5 intracutaneous injections representing less than 10,000 skin test units. Many of these children (60 per cent) slipped back into positive Dick reaction zones by the end of 6 months and the authors concluded from this that larger doses should be administered or reinoculations given at frequent intervals, possibly once or twice a year, to maintain adequate antitoxin levels in the blood. Reactions to the intracutaneous injections were generally mild, consisting of local areas of redness and swelling which persisted for about 24 to 36 hours. Two patients, receiving rather large doses, developed systemic reactions with signs of a generalized rash and fever.

Formalin treated toxin has been employed extensively as an immunizing agent in Massachusetts during the past few years. A preliminary report of the results has been made by G. W. Anderson.³³³ Toxin material containing 150,000 to 200,000 skin test doses per cc was treated with 0.4 per cent formalin until the residual toxicity was 500 to 1500 skin test doses. This was administered in amounts of 0.1 cc., 0.5 cc. and 1 cc. at intervals of 3 weeks. Of a series of 4783 susceptible children less than 15 years of age, 52 per cent were made Dick negative. In 1 community in which there were no concurrent streptococcic infections, the incidence of reversals of the Dick reactions was only 30 per cent. When a large proportion of the children of a community were immunized there seemed to be a general decrease in the incidence of scarlet fever, even though the differences of the attack rates were not much higher in the nonimmunized than in the treated groups. If only a small number of children of a large city were immunized, the author believed that the influence of immunization on the incidence of scarlet fever would be negligible. In such an experiment the treated children experienced much less scarlet fever than the children in the rest of the community or the children of an observed control series. Reactions to the scarlet fever toxoid injections were minimal and the immunization program was readily accepted by the community. It was the author's conclusion that the immunizing ability of the formalized toxin was less than that of the regular 5 injections of raw toxin but the former method produced little reaction in the patients and seemed effective in reducing the incidence of scarlet fever in the treated children and thus decreased the size of epidemics in the community as a whole.

The frequency with which active immunization against scarlet fever has been employed in representative groups throughout the United States has been summarized in the report of S. D. Collins.³¹⁷ The survey of 130 localities in 18 states included a house-to-house investigation of 8758 families representing 39,185 individuals. Only 0.7 per cent of children under 2 years of age had received the injections, but the percentage rose to a peak of 4.1 per cent among children 10 to 11 years of age. The procedure was employed more frequently in private practice among patients of higher economic levels than in clinics; a reversal of the situation in respect to diphtheria and typhoid injections. Scarlet fever immunization was carried out more extensively in the northern than in the southern states. In a limited series of observations, too few in number to have statistical significance, the incidence of scarlet fever was found to be 4.7 per cent in immunized children as compared with a rate of 14.2 per cent in nonimmunized groups.

The *Dick test* may produce an area of immunity in the skin at the site of injection. That this is a specific antitoxic response has been demonstrated by G. F. Dick and G. H. Dick.³³⁴ They had noticed that scarlet fever patients who have had a previous Dick test develop at the site of the injection an area of redness just before the occurrence of the rash and a blanched reaction when the scarlatinal rash develops. This same recrudescence of color may develop at the site of a previous Dick test when immunizing doses of toxin are administered to a patient. The authors injected 10 skin test doses intradermally into a series of patients and 1 to 3 weeks later injected at the same site and at a control area the single skin test dose of the Dick test. Negative reactions occurred at the site of the pre-

vious test in 10 of a group of 12 patients. This local immunity did not prevent the development of a positive reaction when diphtheria skin tests were performed at those sites, nor did heated, inactivated toxin of scarlet fever produce the same local immunity as the potent toxin. The

conclusions reached were that local areas of specific immunity may be produced by the intradermal injection of scarlet fever toxin. When repeated Dick tests are performed, it is advisable to select different areas of the skin for each injection in order to secure accurate readings.

SMALLPOX

By ROBERT A. LYON, M.D.

Vaccination—In a survey of the results of the routine vaccination of more than 1000 college students of Kansas State College, M. W. Husband and D. T. Loy³³⁵ found that approximately 27 per cent of the group had no protection against smallpox. About 18 per cent of the group had not been vaccinated previously and none of them had had the disease itself. An additional 35 per cent of the students had accelerated secondary reactions, so that a total of 62 per cent of the series were susceptible to smallpox in some degree. Approximately 80 per cent of the students came from rural districts and the small towns of the state of Kansas, so that the authors concluded that vaccination is carried out more extensively in cities than in the more isolated localities. It seemed important, however, to carry out routine revaccinations in this age group in order to insure complete protection of each individual.

Complications—The *danger arising from the vaccination of a child with eczema* or from exposing him to an active vaccination "take" has been emphasized recently by G. W. Graves and C. Dowman.³³⁶ They had observed 2 such patients, 1 a child a year of age and another, 2½ years old, both of whom had eczema and had contracted a generalized vaccinia from contact with siblings who

had successful "takes." Severe vaccinia developed on the site of the eczematous lesions and death occurred in both instances. At the autopsy of 1 infant there was found a fatty degeneration of the liver, cloudy swelling of the kidneys and pulmonary congestion without any evidence of encephalitis. To prevent this occurrence, the authors advised that a careful inquiry be made of the presence of eczema or other skin diseases in the family. If such a history is obtained, no member of the family should be vaccinated. As a general measure, an active vaccination "take" might be protected by means of nonrestrictive gauze dressings.

Two cases of *generalized vaccinia* developing in children with eczema have been reported by C. F. McKham and R. A. Ross,³³⁷ which illustrate the dangers of vaccinating children with such skin lesions, and even of vaccinating a sibling of such a patient. One child of 5 years had recovered from an attack of eczema only a week before she was vaccinated. Multiple lesions developed on various parts of the body during the course of the next 4 to 6 weeks, but the child finally recovered. The second patient, 2 years of age, had an eczematous eruption of the scalp which proved to be a fertile field for inoculation with vaccine virus contracted from the vaccina-

tion "take" of an older sibling. In a review of 41 previous reports of this condition, it was noted that vaccinia occurred most frequently (19 instances) in the first year of life when eczema was most apt to occur. Death occurred in one-third of the cases. The generalized infection may develop in the vaccinated patient at any time between the fourth to thirtieth day after vaccination. In patients exposed to the vaccination takes of others, the vaccinia usually developed within periods of 9 to 23 days, most frequently on the sixteenth to twentieth day. Vaccinia is apparently infectious to a high degree and the immunity conferred by such a widely spread eruption is not always a permanent one.

The spontaneous occurrence of *multiple vaccinia lesions* may also occur in vaccinated patients. Such an infant, 7 months of age, has been observed by J. D. Rolleston.³³⁸ In a review of the literature he has found that this disease occurred very rarely and that the prognosis is generally good unless there is a previous dermatitis, especially eczema. It was his opinion that vaccinia is generally a result of spread of the virus by the blood stream.

A patient 11 weeks of age who developed generalized vaccinia has also been described by P. R. Evans.³³⁹ The lesions appeared on the fourteenth day after the vaccination. The primary vaccination "take" had followed its normal course and the secondary papules appeared spontaneously on the extremities without any scratching or the presence of any other type of dermatitis. In a review of previously reported cases the author observed that this condition may occur at any age and following either a primary vaccination or a second or third revaccination. The lesions usually appear on the eleventh to twentieth day after the original vaccination procedure and the prognosis of the vaccinia is generally good except during the first year of life. It has seemed probable that secondary vaccinas are disseminated by the blood stream and are aided by the lack of the skin immunity which usually follows the original vaccination. Ordinarily, no treatment of the disease is necessary unless the infection is very severe and then there is indication for the use of human blood obtained from a patient who has recently been vaccinated and is considered as immune.

SYPHILIS IN CHILDREN

By ROBERT A. LYON, M.D.

Congenital Syphilis

The occurrence of congenital *syphilis in the third generation* has been a matter of speculation for many years. The patient reported by J. C. Clark³⁴⁰ was a young negress, 18 years of age, who had hutchinsonian teeth, mulberry molars, a positive serological test and a very suggestive family history of a luetic infection of the mother. An infant born of this patient had hemorrhages of the nose,

mouth and anus on the second day of life, a positive serological test of the blood taken from the cord at birth and from the jugular vein on the tenth day of life.

Syphilitic infection of 2 children of seronegative mothers has been reported by J. R. Waugh.³⁴¹ The children, both 14 years of age, had definite evidence of congenital syphilis with involvement of the eyes and teeth and positive serologic tests. The mother of one child was 37

years of age and the other mother was 48 years old. Neither had had any anti-syphilitic treatment, and they were free from symptoms and had negative serologic reactions. These 2 cases occurred in a total group of 78 mothers of 89 syphilitic children. Six other mothers of this series were also seronegative but had received antisyphilitic treatment. The author quoted other studies which have indicated the benign course which syphilis follows in the pregnant woman. Whether or not the pregnancy was responsible for the spontaneous cure of syphilis in the 2 cases above was thought to be a questionable matter.

Diagnosis—Although the diagnosis of syphilis in children is frequently made from the serological reaction only, it must be borne in mind that mistakes can be made by this method. The observations of H. B. Rothbart⁴² have included a series of 11 children between the ages of 19 months and 13 years who had positive Kahn reactions at first but became negative spontaneously. Only 2 of these cases had received antisyphilitic treatment, which was small in amount but probably sufficient to have changed the reaction. From previous reports, it has been noted that other diseases, such as tuberculosis, malignant neoplasm, fever, menstruation, jaundice and pregnancy, may give falsely positive serological tests. In the group reported by the author, some type of infection, either acute or chronic, was present in all cases except 1 and it may have been these diseases which made their serologic tests positive temporarily. In the absence of a positive family history or any other evidence of syphilis, it would seem wise to repeat the serological tests in patients with positive reactions with the supposition that negative results will be obtained within a period of time. Such children should not be treated until it is definitely

proved that they have the syphilitic infection.

Quantitative Wassermann reactions have been employed to differentiate true syphilitic infections of newly born infants from the falsely positive reactions resulting from the transfer of antibodies from the mother. A. U. Christie³⁴³ has employed this test in 14 infants. With dilutions of the serum the routine Wassermann was performed in the usual manner, and the reagin content of the serum was expressed in units of the maximum dilution giving a positive result. By following such tests in the groups of infants born of syphilitic mothers, the author was able to demonstrate a decreasing titer in 11 of the patients until they became negative in an average period of about 2 months. These infants had obtained antibodies by passive transfer from their mothers and did not develop active syphilis. The remaining 3 patients tended to develop their own antibodies and the titers rose until they showed clinical evidence of syphilis. By quantitative tests, the true syphilitic infants might be detected early and treatment instituted while the falsely positive group may be observed frequently but not require antisyphilitic therapy.

Treatment—Adequate treatment for early congenital syphilis should include 24 or more doses of *neoarsphenamine* and 30 or more injections of a *bismuth* or *mercury* compound, according to the observations of H. R. Foerster.³⁴⁴ The treatment should be continued for a period of at least 2 years, except possibly in the case of infants who have had no symptoms. Older children should be treated for at least 3 years with a corresponding increase in the number of injections. About 65 per cent of his series of patients with early syphilis and only 33 per cent of the later cases had adequate therapy, which emphasized the

importance of social service activity in bringing such patients to the physician, and the need for adequate treatment of the mother during her pregnancy as a prevention of the disease.

Favorable results with *acetarson*e therapy have been reported by E. E. Smith, R. I. Fried and M. W. Everhart.³⁴⁵ Negative serologic results were obtained in 5 of a group of 10 children over a year of age and in 19 of a group of 23 infants. The drug combined with the oral administration of *mercury with chalk* was effective in curing luetic epiphysitis and snuffles. The therapy seemed to be well tolerated without causing any unpleasant sequelae.

Mercury cyanide has been found to be effective in the treatment of *interstitial keratitis* by E. Lesné and D. Ronget.³⁴⁶ In 1 group of 10 children in which the therapy was instituted immediately after the onset of the infection, complete cure without scarring occurred. One of these patients had a relapse when bismuth was substituted for the mercury but recovered when the latter medication was given again. Three additional patients who had had other types of therapy did poorly until the mercury preparation was instituted and then improvement occurred. Two patients whose treatment was started late or was inadequate in amount, developed permanent opacities of the cornea. Mercury cyanide should be given as early as possible in the course of the infection and it was administered intravenously in doses of 0.1 Gm. for a series of 20 injections at intervals of 2 or 3 days. The treatment was frequently prolonged until all symptoms of keratitis had disappeared and then the other customary antisyphilitic drugs were employed. No serious reactions from the mercury cyanide injections occurred in the authors' series of

patients although colitis and stomatitis were noted in rare instances.

Mapharsen has proven satisfactory in the treatment of congenital syphilis of the series of patients observed by E. A. Morgan.³⁴⁷ Forty children, all but 1 over 5 years of age, have been treated with this drug for an adequate period of time to observe its effects. Twenty per cent of the series had reversals of their serologic reactions and 38 per cent showed a reduction in the Wassermann reaction. This arsenical was administered intravenously at weekly intervals for 6 treatments and was followed by a course of *mercury* given by inunction or by mouth. The average dosage recommended was 0.5 mg. per kg. of body weight which was reduced to 0.15 to 0.3 mg. for the use in younger age groups. No patient of the above group had received such therapy for more than 16 months and the author believed the results compared favorably with previous antisyphilitic therapy employed in his clinic. Reactions such as nausea, vomiting and headache occurred in 133 instances of a total of 935 injections, and they often developed irrespective of the amount of the drug administered. Jaundice occurred in 1 child, but disappeared spontaneously within 3 weeks.

Fever therapy for syphilitic children has been employed in 5 patients by L. Speker and A. McBryde.¹⁵⁶ The blood serologic reactions were changed in 1 patient and considerable improvement occurred in 1 other child with central nervous system involvement and was followed by a complete disappearance of his spinal fluid reactions. One child with acute interstitial keratitis received temporary improvement of the local condition. It seemed wise to continue the routine antisyphilitic treatment of arsenicals in these children. The fever was induced

TIME AT WHICH PREGNANT SYPHILITIC WOMEN REPORTED FOR ANTISYPHILITIC TREATMENT IN
386 CONSECUTIVE SYPHILITIC DELIVERIES OBSERVED AT THE PHILADELPHIA GENERAL
HOSPITAL OCTOBER 1, 1933, TO APRIL 1, 1936, AS COMPARED WITH THE
EXPECTANCY FOR SYPHILIS IN THE OFFSPRING

Treatment Begun	Number Cases	Percentage of Total	Approximate Percentage of Children Found to be Syphilitic
Before Pregnancy and Continued Without Intermission, up to Time of Delivery	5	1.3	.00
Between First and Fourth Calendar Months, Inclusive	67	17.3	.5
During the Fifth Calendar Month	62	16.0	.35
During the Sixth Calendar Month	86	22.5	.35
During the Seventh Calendar Month	48	12.3	.50
During the Eighth Calendar Month	59	15.3	.70+
No Prenatal Antisyphilitic Therapy	59	15.3	.80+
Total	386	100.0	

(N. R. Ingraham, Jr., Ven. Dis. Inform. 19:125 (May) 1938.)

by radiant energy of seven 120-watt carbon filament bulbs in a cellotex-lined box.

The problem of treating infants of luetic mothers who have latent forms of the disease has been discussed by Bernheim-Karrer.³⁴⁸ In a series of 35 children whose mothers had positive serologic tests, and varying amounts of prenatal treatment, 3 developed symptoms of the disease within the first 2 months of life and 5 were given routine treatment with acetarsone by mouth. The remaining children were observed for periods of 1 to 3 years and remained serologically and clinically negative in respect to syphilis. It was questionable whether the routine treatment of all newborn of serologically positive mothers should be advocated. In certain cases, arsenic therapy may be injurious and the possibility of causing unnecessary damage in well infants must be borne in mind. An instance of spastic tetraplegia with a leptomeningitis and external hydrocephalus was observed in the author's clinic which may have resulted, at least in part, from the oral administration of arsenic.

Prevention—The value of *adequate treatment of the pregnant syphilitic woman* in the prevention of the disease in the newborn has been demonstrated by numerous investigations. The table prepared by N. R. Ingraham, Jr.,³⁴⁹ illustrates this fact.

In spite of the well-recognized importance of early prenatal treatment, some 20 to 40 per cent of syphilitic mothers give birth to infected infants. The postponement of treatment seems to be due to (a) The delay of the mothers in reporting to the prenatal clinics until they are in the sixth or seventh month of their pregnancies, (b) the failure of obstetric clinics to provide antisyphilitic treatment, and (c) the delay which occurs after the diagnosis of syphilis has been made and antisyphilitic treatment is begun.

Of importance also is the early detection and the treatment of syphilis in the newborn infant. The chances of obtaining a serologic cure of the infant are much greater if treatment is begun shortly after birth rather than at the end of the first year.

TUBERCULOSIS IN CHILDREN

By WALDO E. NELSON, M.D.

Pathology—The anatomic changes of the progressive primary tuberculous complex have been described by O. Auerbach.³⁵⁰ This study is based on observations from autopsies of 17 children, whose ages ranged from 9 months to 9 years. Sixteen of these were negro children and 1 was white. In 8 of the patients, the primary foci were located in the lower lobe, and in 9 were situated in the upper and middle lobes. The primary focus was located in the right lung in 9 instances and in 8 in the left lung. The size and appearance of the primary focus depended upon the stage of progression in which it was found. In this series it varied from 1.5 to 6.0 cm. In the early stage of progression the parenchymal focus was smaller than the involved lymph nodes, whereas in the later stage of development, the focus reached the same size and was even larger than the nodes. The progressive primary focus was a large, irregularly demarcated area of caseation with no definite capsule.

The lung tissue immediately surrounding this nodule was pneumonic in character and the pleura overlying the focus was thickened. This might have been the result of a caseous pleuritis which developed from the direct extension of the focus. However, most often there was only a localized fibrous thickening of the pleura overlying the focus. In the later stages the area of caseation sometimes extended to the greater part of a lobe, usually with an accompanying liquefaction. In 1 or more areas the softening of the caseous mass occurred and evacuation of the liquefied material resulted in an irregular shaggy excavation. Cavity formation in the primary focus occurred shortly before death so that the reparative

process in the form of a productive reaction was not extensive.

The capsule which formed the boundary of the primary cavity was not well defined. Large caseous masses formed the inner wall of the excavation and there was incomplete liquefaction. Trabeculae, a constant finding in tertiary excavations, were usually absent in primary cavities. The gross appearance of the remaining pulmonary parenchyma was dependent chiefly upon the stage of development of the primary focus. In all instances in this series in which the focus did not go on to liquefaction, there was evidence of hematogenous tuberculosis in the form of miliary acinous and sublobular foci throughout the lung, but wherever primary cavitation was present the lungs were studded chiefly with large foci in the form of sublobular and lobular areas of caseous pneumonia which were fused irregularly with the surrounding firm tissue and showed little tendency toward encapsulation. Central liquefaction and cavity formation were frequently observed in the bronchogenic caseous pneumonic foci, but once cavitation occurred it was impossible to distinguish foci of bronchogenic origin from those of hematogenous origin. Calcification was not observed in any of the primary foci in this series.

The lymph nodes most extensively involved were those lying along the course of the bronchi and in the angle between the trachea and the bronchi. Although caseation occurred in the lymph nodes of the contralateral side, most extensive involvement was found in the nodes on the side of the focus. They were matted together and often caused pressure on the surrounding structures such as the trachea, bronchus or blood vessels. Lique-

faction of the lymph nodes was not necessarily associated with liquefaction of the primary focus. Softening occasionally occurred in both the focus and in the lymph nodes, but more frequently in one or the other. The lymph nodes sometimes ruptured into the trachea, bronchi or blood vessels.

Evidence of hematogenous dissemination was present in every case. Although caseous hematogenous foci were present in the kidney, adrenals and liver, they were most frequent in the spleen. It is believed that tubercle bacilli usually enter the venous circulation by way of the lymphatics but rarely from the rupture of a caseous focus into the blood stream. Nine of the 17 children died of tuberculous meningitis, and in these tuberculomata were demonstrated in 5 instances. Tuberculous ulcerations of the intestines were found in all instances in which there were cavities in the lungs. The ulcers were extensive and occupied large portions of the small and large intestines.

The observations of M. Brailey³⁵¹ supply information concerning both the degree of calcification in primary intra-thoracic tuberculous lesions as well as the apparent speed of calcification. For periods ranging from a few months to more than 5 years, she observed a series of 158 children who were found to be infected with tuberculosis before reaching the age of 2 years. It was found that calcification appeared in the chest in about 17 per cent of the children 1 year after the discovery of tuberculous infection. At the end of 2 years of observation, calcification was observed in 47 per cent; by the end of 3 years in 62 per cent; and by the end of 4 years in 66 per cent. The proportion of cases developing calcification varied with the extent of the lesions. Within a 4-year period, it was observed in 86 per cent of children who had shown parenchymal lesions, in 67 per

cent of those who had shown a definite tracheobronchial node involvement without parenchymal lesions and in 36 per cent of those in whom no definite lesions had ever been recorded. About one-fifth of the cases that developed calcification had shown no definite lesions in earlier X-rays. In the remaining four-fifths, calcification usually took place on the side of the thorax where the active lesion had been noted, but in 9 per cent it appeared only on the opposite side where no lesion had been seen previously. It was observed that in some instances small deposits of calcium became indistinguishable with time, due to changes in calcified mass, or to its becoming hidden by mediastinal structures. In 1 instance there was apparent absorption with disappearance of a calcified parenchymal nodules within 4 years of its first appearance. In only 1 of 46 cases was any loss of allergy to Old Tuberculin observed.

Diagnosis — *Tuberculin* — The efficiency of the new purified tuberculin product, P. P. D., when employed by the Pirquet technique has been tested by A. H. Steele and H. S. Willis.³⁵² When used in a strength of 10 mg. per cc., P. P. D. elicited reactions in approximately but slightly less than the same incidence as Old Tuberculin. The authors believe that the intracutaneous method is preferable to the scratch or Pirquet technique. However, there are circumstances such as parental objections to "injections" when the Pirquet method may be employed advantageously.

Further studies with the tuberculin ointment patch test are reported by E. Wolff and S. Hurwitz.³⁵³ They found an agreement of 98.2 per cent between the ointment patch test and the intracutaneous test with 0.1 mg. of Old Tuberculin in 1075 observations. Discrepancies occurred only in clinically latent

cases. The ointment test was positive in every case of active tuberculous disease.

The ointment is prepared in the following manner: Regular tuberculin glycerin broth is inoculated with human culture H-37. The cultures are incubated for 4 weeks and then sterilized in the Arnold sterilizer. After sterilization the material is evaporated to $\frac{1}{15}$ of its original volume, the organisms being left in the material. The evaporated and concentrated material is then triturated to a smooth mixture, to which 0.4 per cent phenol is added as a preservative. The control material is prepared in exactly the same manner with the exception that the flasks of glycerin broth are not planted with any organisms. The control in this series consisted of the same lot number of broth, and incubation and evaporation were carried out simultaneously with the cultured material.

The technic of the test is as follows: The area usually selected for application of the ointment is the inner surface of the upper arm, or the paravertebral region between the eighth and eleventh thoracic vertebrae. The skin is cleansed with benzene or ether and dried. A pea-sized drop of the tuberculous ointment is applied on the right side and a similar size drop of the control material is placed on the left side. Each of these drops is covered tightly with a $1\frac{1}{2}$ inch square of ordinary adhesive plaster which is removed in 48 hours.

A new tuberculin patch test has been described by H. Vollmer and E. W. Goldberger.³⁵⁴ The patch consists of a strip of adhesive tape on which a square of filter paper saturated with tuberculin has been placed. Results with this test were found to be comparable with those of the Pirquet test. The authors believe that this patch test can replace the initial intracutaneous test with 0.01 mg. of Old Tuberculin. If there is no reaction to the

patch test, a second test by the intracutaneous method, using a higher dilution of tuberculin, should be employed.

The patch test, according to the authors, has the following definite advantages over all tuberculin tests:

1. It is painless and does not excite nervous children, and a good relation between doctor and patient is thus retained.
2. It consumes less time.
3. It does not involve the use of instruments and their sterilization or trauma to the skin due to injection, scarification or rubbing.
4. It can be carried out without help or by a nurse or by an assistant.
5. In contrast to all other patch tests, it creates a sharply limited area of reaction and prevents an uncontrollable spread of tuberculin on the skin.
6. It eliminates the danger of infection.
7. It has never led to a general or local constitutional reaction.

A diluent which decreases the likelihood of deterioration of tuberculin in weak dilutions has been devised by R. Gottschall and W. E. Bunney.³⁵⁵ The diluent is buffered to pH 7.2 with borax and boric acid and contains 0.04 per cent gum arabic and 0.5 per cent phenol. This diluent was found to stabilize tuberculin when diluted 1:10,000 and dispensed in rubber stoppered hard glass vials of 1 or 10 cc. capacity. This stability was proof against destruction by shaking for 7 days, exposure to indirect sunlight and room temperature for 4 months, or prolonged transportation to warm climate and return.

The question, so frequently discussed, of the relationship between the intensity or size of the skin tuberculin reaction and the presence or absence of an active tuberculous lesion has been investigated by E. M. Lincoln, A. Raja and L. A. Gilbert.³⁵⁶ In a study of 1264 measured tuberculin reactions, they could find no positive correlation between the size and intensity of the reactions and the location of tuberculous disease, the size or activity

of the lesion, or the prognosis. Their data indicate that the reaction to the intracutaneous tuberculin test tends to vary in size and intensity directly with the size of the dose and with the age of the child. They state that it is usually unnecessary and undesirable to repeat a tuberculin test during childhood if it has once been positive, as the test only rarely becomes negative during these years.

Repeated tuberculin tests have been performed in tuberculous patients by J. M. Appel, B. H. Douglas, T. R. Jocz and H. S. Wills³⁵⁷ to determine whether there is any relation between tuberculin allergy and the clinical course of the disease. A considerable number of patients varied greatly in the degree to which they reacted to tuberculin, the variation at times representing an increase and at times a decrease in sensitiveness and practically always without evidence of associated clinical, roentgenologic or other change. Thus the reaction to tuberculin appeared to fluctuate variously but not closely in accord with changes in the patient's condition. The authors were unable to draw any conclusions between the degree of tuberculin sensitivity and activity of the tuberculosis process.

In an effort to determine whether sensitization to tuberculin may be induced in many by amounts ordinarily used in skin testing, W. F. Nelson, A. G. Mitchell and E. W. Brown³⁵⁸ performed repeated tuberculin tests in several different groups of children who either had no reaction or not more than a small questionably positive one in either of 2 initial "screening tests." If tuberculin were shown to be antigenic, tuberculin testing after the initial injection would be valueless for the detection of tuberculous infection. Several groups of children were employed and the length of time varied in the different groups from 8 days to 1 year and the number of tests

from 4 to 14. Within the limits of the amount of tuberculin injected in the various tests of this study, there did not appear to be any evidence that tuberculous sensitization was induced by tuberculin injection. This does not imply that sensitization to tuberculin or to tuberculin protein is impossible, but does indicate that such sensitization will probably not occur from the ordinary use of tuberculin for skin testing purposes.

Bacteriologic—Further evidence that the determination of activity of a tuberculous lesion may at times be made by examination of the gastric washings for tubercle bacilli when the results of other methods are negative, is supplied by J. L. Rothstein.³⁵⁹ In a series of 86 infants and children with positive cutaneous reactions to tuberculin, in whom no recognizable evidence of tuberculosis could be demonstrated on physical or roentgenographic examination, Rothstein demonstrated tubercle bacilli in the gastric washings in 7 (8.14 per cent).

Miliary Tuberculosis—An attempt to determine the reason or reasons why, in some instances and not in others, miliary tuberculosis is shown roentgenographically has been undertaken by P. E. Steiner.³⁶⁰ In patients who died of miliary tuberculosis, a comparison was made of the roentgenograms of the chest with the pathologic changes in the lungs. The number, the average size and the histologic structure of the tubercles in the lungs were taken into consideration. It was found that the histologic structure of the tubercles showed the best correlation with the roentgenographic appearance. The ante mortem roentgenograms were negative in all instances in which the tubercles were epithelioid, whereas when the tubercles contained caseous material or collagen or both the roentgenograms were usually positive. The author knows of no chemical explanation

for this observation. None of the tubercles contained visible calcium by routine stains nor did microincineration of tubercles of the various histologic types reveal any significant quantitative difference in ash. The author suggests that if softer roentgen rays or selective filtration of roentgen rays of certain wave lengths were employed, epitheloid tubercles might produce positive roentgenograms. However, it appears obvious from the above observations that tubercles which are demonstrable roentgenographically by present technic have progressed beyond the epitheloid stage.

Meningitis—A comparative study of the Levinson and tryptophan tests as aids in the diagnosis of tuberculous meningitis has been made by F. X. Giustra.³⁶¹ The author found the Levinson test to be positive in 100 per cent and the tryptophan test in 30 per cent of the cases of tuberculous meningitis. The Levinson test was positive in 16 per cent of the cases of nontuberculous meningitis and the tryptophan test was positive in 8 per cent. There was no significant relationship between the reactions of the Levinson and the tryptophan tests and the sugar, chloride and protein content and the number of white blood cells of the spinal fluid. The author concludes that the Levinson and tryptophan tests are not without discrepancy and should not be considered important aids to the present routine methods of diagnosing tuberculous meningitis.

An instance in which tuberculous meningitis resembled diabetic coma is reported by L. L. Krafchik and L. B. Slobody.³⁶² A diagnosis of diabetes mellitus was made on the basis of the child's sudden lapse into stupor, negative tuberculin test, negative spinal fluid, family history of diabetes and the presence of infection associated with hyperglycemia, glycosuria and acetonuria. Later, with

a deepening coma in spite of treatment with insulin, the appearance of convulsions, and a positive spinal fluid, the diagnosis of tuberculous meningitis became apparent.

Determination of Tuberculous Activity—A clinical study has been carried out by W. A. McGee³⁶³ to determine the relative value of the Schilling differential count, the sedimentation rate and the lymphocytic-monocytic ratio for the determination of activity of tuberculosis in children. In the author's experience, greater prognostic aid was obtained from the Schilling count and the sedimentation rate than from the lymphocytic-monocytic ratio *per se*. In cases of moderately or far advanced tuberculosis, the Schilling count and the sedimentation rate more or less paralleled one another. When the tuberculous infection was slight, the shift as shown by the Schilling count was usually slightly elevated, while the sedimentation rate was generally normal. From a practical standpoint, the author felt that the Schilling count had certain advantages over the sedimentation test. The use of Giemsa's stain rather than the Wright stain is recommended, since more detailed cellular structure is visible. It is stated that a combination of the shift (Schilling) percentage and the progressive changes in the percentage of lymphocytes and monocytes gives the optimum prognostic information. Such a combination is also said to give a clearer idea of the extent of the infection. It is cautioned that laboratory tests should in no way be used to replace the clinical and roentgenologic examinations but should be used regularly in conjunction with them.

Immunity and Prophylaxis—In an article entitled "The Latent or Smoldering Stage of Tuberculosis," J. A. Myers³⁶⁴ reaffirms his belief in the danger of primary infection by the tubercle

bacillus. He maintains that this is not because of the initial infection *per se*, but because of the induced sensitization from it. He suggests that attempts to control tuberculosis should be directed toward prevention of exposure to the tubercle bacillus. The following excerpts are from his article:

"A positive tuberculin reaction informs us with certainty that a primary complex is developing or has developed somewhere in the body, even though all other phases of the examination during life fail to reveal its location . . . Because we cannot locate lesions by our crude methods of examination, it does not suffice to say that they are of no significance; and, because they are producing no symptoms, it does not suffice to say that they are not progressive

" . . . Except for the acute forms of reinfection types of tuberculosis such as meningitis, miliary disease and pneumonia, there is apparently quite a long period of time between the laying down of the primary complex and the development of reinfection forms of tuberculosis of clinical significance

" It appears that regardless of the age in life when tubercle bacilli attack the body, there is usually no evidence of a chronic form of clinical disease over a long period of time, at least many months and more often many years or even decades. Indeed there is nothing more spectacular in the whole realm of disease than the ability of the human body to control tubercle bacilli when they first make their attack, regardless of such factors as age, race, nationality and home conditions

" . . . The long period of time that is required for tuberculosis to develop into clinical disease in the human body is probably responsible more than anything else for the absence of symptoms and illness during the period of childhood and adolescence

" The period of latency in tuberculosis does not end with the beginning of adolescence in the majority of human beings who develop the first infective type of disease. Latency continues in the bodies of many persons and even animals throughout the span of life. Among our group of children with positive tuberculin reactions, approximately 10 per cent developed the reinfection type of disease and were ill or dead by the time the majority was or should have been reached. If the morbidity continues at the same rate or is even somewhat

retarded, at least 20 per cent of these children will fall ill before they have lived out the span of life. Many of the remainder will continue to carry their latent or smouldering disease.

" . . . As long as we allow communicable cases of tuberculosis to remain in our communities, smouldering disease will develop among the contacts regardless of age, and as long as smouldering tuberculosis is allowed to develop in the bodies of human beings, we will have a morbidity and a mortality from this disease, regardless of age. . . .

"Only recently we have come to consider seriously the potentialities of smouldering tuberculosis during the period of childhood. At one time we even looked upon the presence of this disease in the body of a child as an asset because we thought it to be a valuable immunizing agent. Now we know that once the primary complex has been allowed to develop, as manifested by a positive tuberculin reaction, there is no treatment of any avail. Immunity does not develop sufficiently to destroy the tubercle bacilli. No treatment that we know, such as long period of strict bed rest or even collapse therapy, destroys the tubercle bacilli in the lesions of the primary complex. Moreover, we have no practical method of permanently desensitizing the tissues of such persons

"Our problem is no less significant than that of the veterinarian, but where he solves it at once, we must wait for further developments, that is, we must keep close watch for the development of the destructive type of disease so that, if and when it occurs, treatment may be instituted before it becomes communicable or causes illness"

In an effort to determine the effect of primary tuberculous infections upon subsequent morbidity and mortality of tuberculosis, G. Herlitz³⁶⁵ has followed 1457 children for periods ranging from 5 to 23 years, or for an average of 13.4 years. The children were divided into 2 groups, those with positive tuberculin reactions and those with negative reactions. From his observations he concludes that the child with a positive tuberculin reaction is more likely to have active tuberculous disease during the next 10-year period than is the child of

the same age who has a negative tuberculin reaction. He also states that this greater liability to tuberculous disease persists throughout the first 3 decades of life.

A simple and economical method for detecting households that harbor patients with open tuberculosis is proposed by C. A. Stewart.³⁶⁶ The method involves the routine use of the intracutaneous tuberculin test but limits the use of the more expensive procedures, such as roentgenologic examinations, to the tuberculin-positive members of homes in which infected children are present. The economy accomplished in this manner appears to make the plan suitable for general use in private practice.

B C G—Since the development of allergy to tuberculin following vaccination with B C G is considered, correctly or incorrectly, to be one of the means for determining successful vaccination, the observations of C. Kereszturi, H. A. Rosenberg and W. H. Park³⁶⁷ are of interest. The time and the degree of development of allergy to Old Tuberculin were observed in 292 children vaccinated intracutaneously and in 41 vaccinated subcutaneously. Intracutaneous tuberculin tests were made at weekly intervals, employing 0.1 and 0.2 mg of Old Tuberculin. The minimum reaction considered positive was an area of induration 10 mm in diameter. Relatively more of the intracutaneous group developed a positive tuberculin reaction than of the subcutaneous group, 80 per cent and 62 per cent, respectively. Allergy developed sooner in the intracutaneous than in the subcutaneous group. The highest incidence of allergy in each group occurred at the end of the sixth month. After this time there was a decrease in the number of positive reactors. The percentage of positive tuberculin reactors at the end of the first year fol-

lowing vaccination was 75 per cent in the intracutaneous group and 50 per cent in the subcutaneous group; at the end of the second year, 45 per cent and 36 per cent; at the end of the third year, 42 per cent and 30 per cent, respectively. In the intracutaneous group, a 0.15-mg. dose produced a greater incidence of allergy than smaller doses of B C G. Larger doses showed no advantage over the 0.15-mg. dose. The incidence of the development of allergy was not influenced by the age of the patient at the time of vaccination. It was found that a direct relationship existed between the incidence of the development of allergy and the severity of the local reaction as well as the severity of the reaction of the regional lymph nodes. The age of the vaccine (1 to 10 days) did not influence the incidence of positive tuberculin reactions. Relatively more cases exposed to open tuberculosis either before or after vaccination became positive to the tuberculin test than those not exposed. Some of the children failed to develop allergy to Old Tuberculin despite several vaccinations with B C G.

Heat-killed Vaccine—Experiments have been carried out by E. L. Opie and J. Freund³⁶⁸ to determine if dead tubercle bacilli can be used to replace the living attenuated microorganism (B C G) as a means of protection against tuberculous infection. Their data indicate that when heat-killed tubercle bacilli were repeatedly injected into or below the skin of rabbits, their resistance to infection with virulent tubercle bacilli was increased. Protection against tuberculous infection following the administration of killed tubercle bacilli to rabbits appeared to be only slightly less than that produced by B C G. The addition of certain antigens, notably heated horse serum, increased the protection given by heat-

killed tubercle bacilli so that it approximated that conferred by B C G.

Allergy vs. Immunity—In recent years it has been suggested that allergy and immunity to the tubercle bacillus are either unrelated phenomena or perhaps are even antagonistic. That this is still an unsettled question is apparent from the observations of H. S. Willis and C. E. Woodruff³⁶⁹ In their series, allergic desensitized guinea pigs experienced a delay of several weeks (after reinfection) in the development of tuberculosis. This delay, they believe, has been mistaken for retained immunity. Animals which were prevented from developing allergy by injection of tuberculin were unusually susceptible to tuberculosis and developed what they state is probably the most marked degree of tuberculous pneumonia yet produced in experimental animals. From these observations they conclude that it is unsafe, for the present, to conclude that the phenomena of allergy are an essential part of the mechanism of defense against tuberculosis.

A study of the effect of allergy upon tuberculous bacillema has been made by J. P. Duchane³⁷⁰ The author has devised a method for the determination of tuberculous bacillema and has applied this to determine the differences in allergic and nonallergic animals. In this instance, the animals were made allergic by B C G vaccination. It was found that there was a more or less constant bacillema in nonallergic animals in contrast to an inconstant bacillema in the allergic animals. Tubercle bacilli injected into the general circulation tended to disappear from the blood much more rapidly in allergic than in nonallergic animals. This clearing process required about 10 days in the nonallergic whereas in the allergic group it occurred within 24 hours. Allergic animals showed

an increased ability to anchor and retain bacilli which had entered the general circulation during the course of the disease. Allergy would thus appear to reduce the danger of dissemination by way of the blood.

Treatment—While there is some disagreement regarding the need or efficacy of *collapse therapy* in primary pulmonary tuberculosis in children, there is rather general agreement that such treatment should be employed in children as well as in adults when active, progressive lesions are present. The experience of M. Siegel and B. Singer³⁷¹ indicates that *pneumothorax* and other means of effecting adequate collapse of the lung are important measures in the treatment of pulmonary tuberculosis in children. According to their observations the results vary considerably with the nature and extent of the lesion, the degree and duration of collapse, and the duration of observation.

Collapse therapy was instituted only for children with open lesions. The sputum of all the children contained tubercle bacilli, and a cavity was visible in the roentgenograms of 95 per cent of the cases. The types of lesions could be listed, in the main, under 4 headings as follows:

Type of Case	Number of Cases
Isolated, infiltrative tuberculosis, unilateral	38
Isolated, infiltrative tuberculosis with contralateral spread	35
Disseminated tuberculosis	17
Advanced bilateral tuberculosis with bilateral cavities	15

In most instances residuals of the primary infection were visible on roentgenologic examination as calcified areas in the hilar nodes or as solitary calcified foci in the parenchyma which might be interpreted as calcified primary lesions. The children who had only an active

primary lesion were not given collapse therapy.

Collapse therapy is generally employed for tuberculous children over the age of 10 or 11 years, in whom open pulmonary lesions begin to develop in increasing number. Between the ages of 3 and 10 years, when the mortality curve of tuberculosis is at its lowest, collapse therapy is not frequently employed because the disease during this age period is usually benign and improves spontaneously. Therefore, the beneficial effects of collapse therapy are difficult to evaluate. Its use for children under 3 years of age, in whom pulmonary tuberculosis is a serious problem, is hampered by technical difficulties and by the nature of the primary lesion, which either heals spontaneously or disseminates so rapidly as to be beyond the aid of local measures. Further, the frequency of bilateral lesions and the low vital capacity in early childhood restrict the use of collapse therapy during this period.

The ages of the treated children in this series varied from 5 to 15 years. Fourteen were from 5 to 10 years of age, 21 were 11 or 12 years of age, and 17 were 13 years of age or older. Up to the age of 10 there was an equal number of males and females. Above this age there were approximately 4 times as many girls as boys.

When it became apparent that artificial pneumothorax alone would be unsuccessful on account of pleural adhesions or other complicating factors, other procedures were employed. These included internal pneumolysis, thoracoplasty, phrenicectomy and oleothorax.

Of the 105 children who were treated between 1928 and 1936, 40 were improved, 33 remained unimproved, and 32 died. The control group consisted of 87 children with open lesions who re-

ceived no form of collapse therapy. Between the years 1929 and 1936, 83 of these children have died, 1 is unimproved and 3 are improved. Thus there is a distinct difference between the results of the treated and the untreated children.

The results were determined by the effect of collapse therapy on the cavity and on the presence of tubercle bacilli in the sputum or in the gastric washings. If the cavity disappeared and the sputum became negative and remained negative for more than 4 months, the child was considered as improved. If the cavity remained open, or if the sputum was positive, the patient was considered as unimproved.

The results of collapse therapy in patients with various types of lesions were as follows. Of the patients with isolated infiltrative tuberculosis (unilateral), 60 per cent improved; of those with infiltrative tuberculosis (with contralateral spread), 22 per cent improved, of those with disseminated tuberculosis, 29 per cent improved. The effect of the degree of collapse on the outcome depended in part on the type and extent of the lesion. On the whole, however, the following results were obtained with varying amounts of collapse. With a small amount of collapse (less than 50 per cent), 15 per cent of the patients improved, with a moderate amount (50 to 75 per cent), 30 per cent improved, and with a large amount (over 75 per cent), 50 per cent improved.

The best results were obtained among children with unilateral isolated infiltrative tuberculosis in whom a large amount of collapse could be obtained. When the infiltrative lesion had spread to the other side, the chances of improvement were considerably reduced. Regression of the contralateral process was seen in only 12 per cent of the cases in which bilateral lesions were treated

on 1 side only, while progression occurred in 53 per cent of these cases. The authors now feel that unilateral collapse therapy is inadequate in such cases and that collapse on both sides is required. By means of bilateral collapse therapy, they were able to increase the number of improved children.

Several children improved after thoracoplasty. Extensive thoracoplasty proved undesirable on account of the marked kyphoscoliosis that developed. The degree of scoliosis that developed after a partial thoracoplasty was not sufficiently marked to constitute a contraindication to the operation.

Moderate or large amounts of pleural effusion developed in the course of pneumothorax in 28 cases. Tubercle bacilli alone were found in 9 cases, pyogenic organisms and tubercle bacilli in 4 cases, and pneumococci in 1 case. The fluid was resorbed in only 2 of the 13 cases in which either tuberculous or mixed infections were present.

Prognosis—Further statistics on the state of children infected with tuberculosis during the first 5 years of life is presented by H. A. Rosenberg and C. Kereszturi.³⁷² It should be understood that such statistics taken from different groups of patients will differ considerably. In addition to the age at the time of infection, such factors as the length of the period of exposure, the living conditions and the general health of the child must be taken into consideration. In this group of 348 infants infected with tuberculosis during the first 5 years of life and observed for from 1 to 9 years, the rate of death from tuberculosis was 9.1 per cent. The rate of mortality from tuberculosis among the negro children was approximately twice that of white ones. The rate of deaths from tuberculosis among 175 children infected during the first year of life was 14.8 per

cent, and 10.2 per cent for the 59 who were infected during the first half of the second year. The rate was 43.7 per cent for those infants infected during the first 3 months of life. No deaths from tuberculosis occurred in the group of 114 children infected after 18 months of age. The rate of deaths from tuberculosis was more than 5 times as high in the children with parenchymal lesions in contrast to those with only enlarged tracheobronchial nodes and about 8 times as high as in those who had no roentgenographic evidence of tuberculosis.

The effect of contagious diseases on pulmonary tuberculosis and on the tuberculin reaction in children has been observed by J. P. Nallbant.³⁷³ He found no definite evidence to support the more or less general belief that measles, chickenpox, whooping cough, mumps, scarlet fever and diphtheria have a deleterious effect on pulmonary tuberculous lesions in children. He did, however, find 12 instances of demonstrable increase in the roentgenographic findings at various times during the convalescence in a group of 118 children who had 147 attacks of acute contagious diseases. The author contends that exacerbations or remissions are fairly common occurrences during the course of the childhood type of tuberculosis, and that they may occur in the presence or absence of intercurrent contagious diseases. The remissions observed were in all instances in children with active tuberculous lesions. In no instance was a remission observed in a child with a quiescent or inactive tuberculous lesion. The author is of the opinion that the remissions observed could be safely considered coincidental and unrelated to the contagious disease.

In regard to the effect of the contagious disease upon the tuberculin reaction, the author has data only for

measles, chickenpox and mumps. No change was noted in the tuberculin reaction either during or after the chickenpox. In the case of mumps, 18 of the 24 showed from moderate to marked increase in size and duration of the tuberculin reaction and 2 showed decreased reaction. Of 27 children with measles, 4 became negative to a dose to which they were positive before, but were again positive 2 weeks after the disappearance of the eruption. The author concludes that no definite evidence was found to support the belief that contagious diseases depressed allergy to tuberculin. It should be noted that the author has no data on the effect of scarlet fever, which has been shown to depress the

skin reaction to tuberculin, and that in 4 of 27 cases he noted a temporary state of allergy during measles. In regard to the effect of chickenpox, he is in agreement with most other observers.

Of interest in relation to Nalbant's experience is that of G. F. Mitchell³⁷⁴ who observed the effect of streptococcic throat infection in tuberculous children. Both reports are from the same institution. The author felt that the number of children (14.8 per cent) who showed roentgenographic evidence of increase in their tuberculous infection was definitely greater than was usually experienced in the course of routine check-ups in an equal number of children during a period of 4 months.

WHOOPING COUGH

By ROBERT A. LYON, M.D.

An extreme degree of leukocytosis was observed in a patient with whooping cough by W. J. Pearson and G. H. Newns.³⁷⁵ A boy, 5½ years of age, developed pertussis shortly after the removal of his tonsils and the disease was complicated by bronchopneumonia. The white count rose to as high as 145,000, but dropped rapidly during the next 2 weeks and slowly fell to normal figures. None of the blood cells were unusual types suggesting leukemia.

The cerebrospinal fluids of pertussis patients with or without complications were found to be normal in the study made by J. H. Magnussen.³⁷⁶ A group of 33 children between the ages of less than a year to over 6 years had attacks of average severity, and 15 had such complications as otitis media, bronchopneumonia and tuberculosis. The cerebrospinal fluids were examined in respect to the type and number of cells present,

the pressure, the bacteriologic content and the sugar and albumin levels. In both groups of patients the fluids were normal.

Diagnosis—The early diagnosis of whooping cough by means of bacteriological examination of *cough plates* or of *pharyngeal swabs* has been recommended by E. A. Straker and J. S. Westwater.³⁷⁷ The cough plate method was employed in a series of 125 patients with whooping cough in the early catarrhal or spasmodic stages. Positive results were obtained in 98 patients or 78.4 per cent of the group. The best results were obtained in the first 2 weeks of the disease and by the fourth week of the infection only half of the number of patients showed positive cultures. A study was also made of cultures taken with sterile cotton swabs stroked across the top of the epiglottis. In a series of 47 patients, positive results were obtained in 47 per cent by the swab

method and in 70 per cent by the cough plate method. In 12 instances the cough plate was positive and the pharyngeal swab was negative. It seemed to the authors that this swab method of obtaining a culture, which was easier and more rapid, might deserve further investigation. In the cough plate method, the best results were obtained when the media was enriched with at least 50 per cent fresh fibrinated horse blood although other investigators have been satisfied with smaller percentages of blood. Proper technic in obtaining the cough plate cultures and in isolating the organism is an important factor in the success of this method of diagnosis of pertussis.

The cough plate method of diagnosis of pertussis has been used for 4 years with a high degree of success by N. Silverthorne and D. T. Fraser.³⁷⁸ During the first week of the disease the plates of 94 per cent of the patients contained the specific bacilli. The relative frequency of positive bacteriologic diagnoses in the various weeks of the disease in a series of 568 cases is reported in the following table.

ANALYSIS OF 568 CASES OF CLINICAL
WHOOPIING COUGH

Week of Disease	Cases Examined	Cases Positive	Percentage Positive
1st	183	173	94
2nd	187	162	86
3rd	102	49	48
4th	55	17	30
5th	23	1	4
6th	15	4	
7th	1	0	
9th	1	0	
12th	1	0	

(Silverthorne, N. and Fraser, D. T. *Canad. M. A. J.* 38: 557 (June) 1938.)

Since the exposure of the plates was left in the hands of various persons, this large number of successful results would indicate that the procedure is a very practical one.

Bacteriology—Recent experiments seem to indicate that the anatomic changes of pertussis can be caused by the Bordet-Gengou bacillus alone. The work of D. H. Sprunt, D. S. Martin and S. McDearman³⁷⁹ has shown that this microorganism can produce the typical lymphocytosis and interstitial pneumonia of pertussis in monkeys and rabbits. Intratracheal inoculations of the Bordet-Gengou bacillus into monkeys produced a characteristic lymphocytosis in 6 of a group of 9 animals and an interstitial pneumonia developed in 8 of the series. Lymphocytic reactions occurred in all of a series of 17 rabbits inoculated in the same manner, while little or no response followed the inoculations of a virulent pertussis bacilli or of Friedlander's bacilli. The interstitial pneumonia of the monkeys occurred in varying degrees of severity but did not seem to be the result of other invading bacteria, even when the lungs were previously damaged by the injection of staphylococcus toxin.

Additional evidence that the pertussis bacillus is the sole cause of whooping cough has been furnished by the experiments of M. Gallavan and E. W. Goodpasture.³⁸⁰ They were able to infect chick embryos with *H. Pertussis* and produce pulmonary lesions identical to those caused by the infection in man. The bacilli grew on the ciliated borders of the respiratory epithelium and caused inflammation and necrosis of the middle and basal epithelial layers. Cellular exudation occurred within and around the bronchioles and pneumonia of an alveolar and interstitial type developed.

The specificity of the pertussis bacillus in producing whooping cough has been affirmed by the experiments of W. L. Bradford.³⁸¹ Intratracheal injections of the bacilli produced interstitial changes and a mucoid exudate in the lungs of animals typical of pertussis pneumonia,

and an increase in the number of lymphocytes in the blood. The bacilli could be recovered from the lung tissue 10 to 20 days after inoculation.

Treatment—One of the most effective methods of treatment of whooping cough in its early stages is the injection of a *pertussis endotoxin*. Encouraging results with this therapy have been reported by A. R. Thompson.³⁸² He ground in a ball mill the pertussis bacilli of a strain of known potency and prepared an extract which contained the products of 10,000 million pertussis bacilli per cubic centimeter. This material was injected in initial doses of 0.25 to 0.5 cc., depending upon the age of the child, and in increasing amounts daily or every other day until 10 to 12 doses had been given. The dosage was increased until some focal reaction was obtained which rarely required more than 2 or 3 cc. in all. In a few instances the occurrence of a local reaction at the site of injection seemed to stimulate the development of severe pertussis symptoms and it was concluded that the occurrence of any local reaction was an indication that adequate amount of the vaccine had been given. In a series of pertussis patients observed in a hospital, 124 received treatment and 248 served as a control group. Mild attacks were slightly more frequent among the treated group while moderate and severe attacks were somewhat more frequent among the control group. There was also some evidence that the course of the disease was shortened by the administration of this vaccine. In order to obtain these effects, it was usually necessary that the treatment be given early, preferably during the first week or 2 of the catarrhal symptoms. Patients treated late in the disease did not seem to respond in any way to the vaccine. Skin reactions obtained by the intradermal injection of this vaccine were positive in

much higher percentages among individuals who had had the infection than in control series of patients who had not had the disease.

Favorable results with vaccine therapy have been reported by A. Hottinger.³⁸³ A group of 53 infants of an average age of 2 years who received the vaccine early in the course of the disease had milder attacks than a group of children of about 4 years of age, who received no specific therapy. In older children and in adults, the results of vaccine treatment were less favorable. Prophylactic treatment of 49 infants averaging 11 months of age did not produce an absolute protection against the illness but the attacks seemed to be milder.

Treatment of pertussis patients with *Vitamin C* has been tried by M. J. Ormerod and B. M. Unkauf.³⁸⁴ Previous experiments had shown an inhibitory effect of ascorbic acid on the growth of cultures of pertussis bacilla. The vitamin was administered in doses of 150 to 500 mg. daily to 9 children in various stages of pertussis and the clinical course of the disease seemed to be considerably shortened.

Further tests with this type of therapy by M. J. Ormerod, B. M. Unkauf and F. D. White³⁸⁵ have indicated that most patients with whooping cough excrete very small amounts of vitamin C in their urine and this was believed to be an indication of an exhaustion of the tissue supply. The addition of ascorbic acid to the diet increased the amounts eliminated. Divided doses of the vitamin seemed to be more effective than a single large dose in maintaining body levels at a proper level. The dosage finally adopted was the administration on successive days of 350, 250, 200, 200, 150, 150, 125, 125 and, finally, 100 mg. as long as necessary, regardless of the age or weight of the patient. The treatment of 17 additional

patients with pertussis by this method gave very favorable clinical results.

Sulfanilamide had no therapeutic value in combating pertussis infections of mice in the experiments of P. Gross, F. B. Cooper and M. Lewis.³⁸⁶ Both treated and untreated animals died as the result of injections of pertussis bacilli.

Immunization—The experience of Evanston, Illinois, in widespread immunization against whooping cough has been reported by L. Sauer.³⁸⁷ A series of more than 2700 children were given the inoculations according to the Sauer method over a period of 3 years. Of this group 128 were exposed to the disease subsequently and 6 developed the infection, but the majority of this latter group were more than 2 years of age when they had received the immunization. The average age of the other children, especially those injected in welfare clinics, was 10 months. The author suggested that a larger amount of vaccine, probably 10 cc. in all, should be administered to children of 2 years or more of age. The incidence of whooping cough in that city has been reduced considerably. The average number of cases for the entire city for 4 years from 1930 to 1933, inclusive, was 325 a year and for the next 3 years, 1934 to 1936, the average was 290.

A group of 335 infants, 3 to 12 months of age, who received the Sauer vaccine, were observed for a period of 15 months by C. A. Stewart and E. S. Platou.³⁸¹ Two of these infants developed the infection approximately a year after the immunization. One had a moderately severe infection and the other a mild one.

Favorable evidence that vaccination against pertussis is an effective procedure has been furnished by the observations of N. Silverthorne and D. T. Fraser.³⁷⁸ Their results have been tabulated in the following table.

ANALYSIS OF VACCINATED AND CONTROL CHILDREN

<i>Controls</i>			
Total 355
Total followed		.	161
Total contacts			
Direct	.		27
Total developed whooping cough		.	23
<i>Vaccinated</i>			
Total	853
Total followed		.	747
Total contacts			
Direct		.	41
Indirect		..	50
Total developed whooping cough		..	2*

(N. Silverthorne and D. T. Fraser, *Canad. M. A. J.* 38: 557 (June) 1938.)

The authors have been able to increase the virulence of pertussis infections in mice by inoculating the microorganisms in combination with mucin. As a result of the development of this lethal test of the bacilli in mice, experiments in protection of these animals with vaccine have been made possible. The injection of vaccine into mice enabled all but 6 per cent of the animals to survive inoculation with freshly isolated strains of the pertussis bacilli and mucin while 88 per cent of a control unvaccinated group of mice died as a result of this procedure.

The protection afforded by the Sauer vaccine seemed to persist in some degree for a period of at least 2 years in the patients observed by J. G. Kramer.³⁸⁸ An outbreak of pertussis in an institution exposed 9 children who had received a complete series of vaccination 2 years previously, 12 children who had not been treated and 8 who had had the infection previously. All of the untreated patients contracted moderately severe infections and the vaccinated children had milder attacks as a rule. Interesting to observe was the universal involvement of all of the children who

* One of these patients had not completed the required inoculation.

had had pertussis previously. They developed mild coughing paroxysms for periods of 1 to 3 weeks.

Controlled observations of pertussis vaccination have thrown some doubt on its effectiveness. A group of 101 children of a tuberculosis sanitarium were vaccinated by M. Siegel and E. W. Goldberger³⁸⁹ with Sauer vaccine containing 80 billion bacilli. The majority of these children were under 6 years of age at the time of vaccination. A group of 82 children of approximately the same age served as a control series. Seventeen of the vaccinated and 19 of the unvaccinated children, who had not had the disease previously, were exposed 1 to 21 months later to the infection. Nine of the vaccinated and 11 of the control series contracted the illness. The disease seemed to run a somewhat milder course in the vaccinated series. The authors discussed the possibility of some interference of the vaccination process by the presence of tuberculosis in these children or the chance that the pertussis infection might have been an unusually severe type. Neither explanation of the failure of the vaccination method could be substantiated and the conclusion was reached that controlled experiments of this type might give more adequate information of the value of this preventive method.

Little is known today of the antigenic material present in whooping cough vaccine. At the present time, most of the vaccines contain either the endotoxin, the exotoxin, or both. Recently an investigation of the immunizing fraction contained in the pertussis bacilli has been conducted by J. C. Cruickshank and G. G. Freeman.³⁹⁰ After obtaining a strain of pertussis bacillus which was definitely pathogenic to mice in known quantities, the authors attempted to extract a portion of the culture by subjecting the bacteria to digestion with trypsin. The

digest was then centrifuged and filtered and the fraction obtained was precipitated by the addition of 68 per cent alcohol. This precipitate, which contained only 10 to 15 per cent of the original weight of the bacteria and was low in protein content, was used in large doses to immunize mice. A high degree of protection against the infection developed in the animals.

The intranasal instillation of pertussis vaccine has been suggested as a method of immunization against that disease. The experiments of P. H. Long and E. A. Bliss³⁹¹ have indicated that the introduction of either living or killed organisms into the nasal passages of rabbits causes the development of complement fixation antibodies in the rabbit's serum which last as long as 2½ months. The experiment with killed antigen was also attempted in 10 adults and 1 child. In 7 of these patients the complement fixation reaction was greatly increased and the authors were inclined to believe that the method was of some value in the production of an immunity, although they have questioned the accuracy of the complement fixation reaction as an indication of true immunity to the disease. Further investigations are in progress.

A vaccine of pertussis bacilli treated with formalin has been employed for immunization by M. L. Blatt, I. M. Levin and I. E. Schapiro.³⁹² A total of 30 billion organisms were injected either subcutaneously in 3 weekly doses or intracutaneously in 5 doses at intervals of 3 or 4 days. In a series of 178 children seen in private practice, the subcutaneous inoculations caused mild local reactions in 40 per cent of the group and various degrees of systemic reaction in 5.6 per cent. Whooping cough developed later in 8 per cent of the total number of treated patients which was less than the expected case rate of the community as a whole.

The intracutaneous method of administration was used in another series observed in private practice and the general results seemed to be as favorable and reactions less numerous than in those who received subcutaneous injections. A second group of institutional children were vaccinated in close relationship to exposure to the disease. Some protection or delay of infection was noted in a few instances but a longer time of observation was required to determine the duration of the immunity.

It has been suggested that an added immunity to pertussis might be obtained by injecting small doses of a *precipitated antigen* which would be absorbed more slowly over a long period of time. A preliminary trial with such a vaccine has been made by W. T. Harrison, J. P. Franklin and J. A. Bell.³⁹³ A saline suspension of pertussis bacilli was precipitated with alum and doses of 1 cc. were injected into 82 susceptible children without any severe reactions. A small indurated area at the site of injection persisted for about 1 week. A group of 109, untreated children served as a control series. After 1 year, a survey indicated that 12 per cent of the vaccinated children had contracted the illness as compared with 19 per cent of the control group. As a rule, the attacks in the vaccinated group seemed milder and of shorter duration. Although the observations were limited in number, the results seemed to justify further trial of the new form of antigen.

The development of a *skin test* indicative of a patient's immunity to pertussis has been under consideration for a number of years. The subject has been investigated recently in a series of 1300 patients by A. R. Thompson³⁹⁴ who found that the intradermal injection of Sauer's type of vaccine was of little value as a test. Endotoxin, however, gave positive

reactions, apparently of an allergic type, in 85 per cent of subjects who had had the infection. About 30 per cent of those who had not had whooping cough previously, also gave the reaction which may have been the result of subclinical attacks of the disease. The sensitivity of the patient to the bacterial products seemed to develop in about 10 days after the onset of the symptoms of the disease.

Another immune response of a patient is the increase in the opsono-cytophagic reaction of the blood. This reaction represents the development of an opsonizing antibody in the serum and an increase of the phagocytosing power of the leukocytes. C. Singer-Brooks and J. J. Miller³⁹⁵ have recently tested this reaction in several groups of children. The first group of 40 children was examined before and after injection of pertussis vaccine and a portion of the group was retested 2 to 6 months later. A rise in the opsono-cytophagic reaction occurred but the numbers in the series were not large enough to give results of statistical significance. The reaction persisted for 6 to 9 months in vaccinated groups and similar responses occurred in patients convalescent from the disease. In other groups, phagocytosis was not stimulated by the injection of the undenatured vaccine of Krueger and the reaction was not noted in the control series of patients receiving saline injections. Infants under 18 months of age who had not received vaccine or had the disease had low phagocytic responses. Older infants and children often developed various degrees of phagocytic power but rarely as high as that produced by vaccination. The test does not yet seem to the authors to be reliable for estimation of immunity of a patient but may be applicable for testing the potency of pertussis vaccines.

Similar studies have been conducted by W. L. Bradford and B. Slavin.³⁹⁶ In 49 patients in various stages of convalescence from whooping cough, phagocytosis tended to increase from the third to the eighth month after the onset of symptoms. When the same patients were followed through the course of the illness their reactions increased as convalescence occurred. A comparison of children who had had the disease previously with a control series with negative histories showed that greater amounts were present in the former group. Nonspecific factors, such as fever or artificial thermal treatment, were found to have increased phagocytosis in some patients. The reactions in newborn infants bore considerable relationship to those of their mothers so that the authors believed that placental transfer of these antibodies might take place.

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PHYSICAL THERAPY

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ULTRAVIOLET RADIATION

Artificial Sources of Ultraviolet Radiation

Coblentz¹ in considering the physical aspects of ultraviolet therapy states that according to Morton, Heilbron and Kamm the destruction of vitamin D is the result of excessive irradiation (though not exclusively) by wave lengths shorter than about 2700 angstroms. Reerink and Van Wijk report that irradiation of ergosterol with a wave length of 2537 Å. gives rise to a series of reaction products that differ from that caused by irradiation with wave lengths longer than 2750 Å. By excluding wave lengths shorter than 2750 Å it was possible to convert 60 per cent of the ergosterol into vitamin D before the secondary reaction (destruction of vitamin D) became important. When the wave lengths of 2537 and 2654 Å were included, only a much smaller amount of ergosterol could be converted into vitamin D before destructive action interfered.

No investigations appear to have been made to determine whether after destruction of vitamin D by the shorter ultraviolet wave lengths (from 2480 to 2650 Å), the antirachitic activity can be restored by irradiation with the photochemically effective wave lengths at 2894 to 2967 Å respectively.

In view of the foregoing results, even though no ill effects seem to have been reported, and an excessive exposure is limited by skin tolerance as manifested by the erythematous reaction, the question arises as to the desirability of conducting ultraviolet therapy with lamps emit-

ting an excessive amount of ultraviolet radiation of wave lengths shorter than 2800 Å. For example, in the so-called cold quartz type of mercury vapor lamp, more than 95 per cent of the biologically effective radiation that is emitted is of the wave length of 2537 Å. These short wave lengths have a specific germicidal action and, hence, are useful in dermatology. Nevertheless it is a question whether rays of such short wave lengths should be used in general ultraviolet therapy. In view of this uncertainty, the Council on Physical Therapy does not accept, for home use without the direction of a physician, lamps that emit an appreciable amount of ultraviolet radiation of wave lengths shorter than 2800 Å.

One difficulty in estimating a threshold or minimum perceptible erythema (defined as a reddening of the skin that disappears in less than 18 hours) is that for the longer wave lengths, for a slight overexposure, pigmentation is visible within 24 hours after exposure. Moreover, the minimum perceptible erythema is easily affected by the kind of diet (acid foods increase the erythematous reaction and pigmentation, alkali foods weaken erythema and pigmentation) and also by external conditions. For example, wiping the irradiated skin with benzene or toluene causes the minimum perceptible erythema to disappear and wiping with alcohol, 24 hours after irradiation, causes a reddening of some of the exposures that were invisible. Hence, before making an erythema test the parts that are to be irradiated should be washed with soap and water, thor-

oughly dried, and left untouched for 24 hours or more.

The spectral reaction differs from (and seems less complex than) the visual response in that there are 2 maximums, at 2500 and 2967 Å. respectively. In contrast with the visual response, these maximums are not affected by the intensity or the spectral composition (the "color") of the source. This deduction follows from the close agreement between the observed and calculated erythemato-genic efficiencies of various sources of heterogeneous ultraviolet radiations.

The wave length limits of antirachitic and erythema action are in close coincidence. Hence, since the time of exposure to ultraviolet radiation depends on skin tolerance as indicated by the erythema response, it is apparent that, with the lamps now available in ultraviolet therapy, the time of exposure is limited by skin tolerance.

In response to a request for a simple means of determining whether a lamp emits ultraviolet radiation and in order to protect the public from imposition by purchasing a lamp that emits little or no ultraviolet radiation, the Council on Physical Therapy of the American Medical Association has adopted and, until a more practicable and reliable procedure is proposed, will use the erythema reaction as a basis for judging the effectiveness (the ultraviolet output) of a sun lamp. The Council does not prescribe the dosage, which is left to the judgment of the physician. It requires for acceptance that a lamp for home use sold at a special (advanced) price shall emit ultraviolet of sufficient intensity at a fixed distance (2 feet) to produce an erythema (M. P. E.) in 1 hour—certainly a reasonable requirement.

According to Coblenz¹ in the treatment of rickets by irradiation there is but little difference in the erythemato-genic

and antirachitic efficiencies of the various sources of ultraviolet radiation now in use. Coblenz states that on the basis of the results published by Bunker and Harris, assuming that the spectral antirachitic response in human beings is the same as observed on experimentally induced rickets in rats, the ratio of the calculated antirachitic efficiency of the ultraviolet radiation from various sources is as follows. "Therapeutic C" (poly-metal) cored carbon arc (antirachitic ÷ erythema = 1.35); low voltage, high temperature mercury vapor arc in quartz (Uviarc) 1.14, high temperature, mercury vapor arc in Corex D glass (General Electric Company, S-1) 1.14; low voltage, low temperature, high voltage, low temperature (so-called cold quartz) mercury vapor arc in quartz 1.12 and midlatitude, midsummer, midday, sea level sunlight 0.95.

From this it can be seen that, of the various artificial sources now in use, only with the carbon arc impregnated with metals (Mg.) having a strong emission in the spectral region of from 2700 to 2900 Å is it possible to deliver an appreciably (35 per cent) greater amount of antirachitic radiation than erythemato-genic radiation, in the time fixed by skin tolerance as determined by the erythema reaction.

This does not take into consideration the efficiency of antirachitic action as dependent on the before-mentioned effect possibly of different wave lengths on calcium and phosphorus metabolism, and also on the deactivation effect of short wave lengths on vitamin D, which may militate against long exposures with sources having a strong emission of wave lengths shorter than about 2800 Å, *e g*, the so-called cold quartz lamp, in which over 95 per cent of the activating radiation is in the resonance emission line at 2537 Å. On the other hand,

such a source (cold quartz) permits an overexposure, by the factor of 5 or perhaps more, without causing a painful blister that results from a slight overexposure to sources of ultraviolet having a relatively strong emission of wave lengths of 3100 to 3200 Å. From this it appears that, since the erythema reaction is a measure of skin tolerance, it is indirectly a measure of the effectiveness of the sources of ultraviolet radiation now in use in healing rickets.

Incidentally, this author believes it is of interest to note that the amount of ultraviolet radiation that can be applied practically to milk is influenced by the flavor that is developed, also that the antirachitic quality of the irradiated milk is proportional to the total ultraviolet energy imparted to the milk. By using a carbon arc lamp with cored electrodes containing magnesium, which has a strong emission at 2800 Å, more than 3 times the energy (of wave lengths of 2600 to 3100 Å) could be imparted to the milk before a perceptible flavor developed than with sources that are weak in radiation at 2800 to 2900 Å.

Tuberculosis

Mayer² states that light therapy, both natural and artificial, is of definite value in the treatment of certain forms of tuberculosis. Benefits from light therapy are undoubtedly obtained by patients suffering from tuberculosis of the bones, articulations, peritoneum, intestine, lymph nodes and larynx when the entire body is exposed to carefully graded doses of natural sunlight or to radiation emitted by certain artificial sources of light rays. The beneficial results of such irradiation are due not only to ultraviolet rays. The visible and infrared rays, as well as the conditions of the atmosphere, play a certain part in the therapeutic effect.

In superficial tuberculous ulcerations, healing, if it occurs, is due not directly to the death of tubercle bacilli caused by ultraviolet energy, but to a local inflammatory or immune reaction of a nature still unexplained. Such ulcers may also heal during general body irradiation when the ulcer itself is unexposed.

Bones and Joints — Mayer² states that in tuberculosis of the bones and articulations it is generally agreed that suitable, graded exposure to natural sunlight is most effective in promoting the healing accomplished by orthopedic and other measures. Exposure to artificial sources of radiation is valuable as second choice. Surgery, solar and artificial light therapy, braces, even in some cases the much maligned plaster-of-Paris cast, all have their place in the treatment. It is not to be expected that light therapy will produce new cartilage in place of that which has been utterly destroyed, it does not make the process of fusion less necessary than it has been hitherto, but it can help this develop. It is wrong to expect that its use will bring about regeneration of bone equal to that of a few vertebral bodies when they have been destroyed, but when this has occurred and a gibbous deformity exists, light therapy has aided orthopedic treatment in fusing these diseased surfaces, especially when employed together with postural treatment. Surgical fusions are less commonly performed on children under 12 years of age. If performed on adults or children, the disease must first show some evidence of retrogression, thus surgery is to help nature.

Indications for surgical intervention may depend on economic and social conditions, the age of the patient, the joint involved, their number and the stage and extent of the disease, involvement of other organs, such as the lungs

and kidneys, and complicating abscesses or sinuses. Surgical fusion is to be seriously considered in the presence of advanced joint destruction. Restoration of function may occur in the synovial form of joint tuberculosis, even in the presence of large effusions; but complete functional return of motion in a joint is doubtful when the bony parts have been destroyed to a marked degree. Following operation, patients are still treated from 1 to 2 years, and during this period heliotherapy plays an important part. Both mercury arc in quartz and the carbon arc irradiations employed as general and local exposures for prolonged periods of time have proved helpful aids. Small joints yield more quickly to conservative treatment than large ones. The knee joint is especially refractory, and particularly obstinate are old fistulas of the spinal column, pelvis or hip.

Genitourinary System—According to Mayer² genitourinary tuberculosis deserves a trial of such treatment in combination with other measures. If *unilateral renal tuberculosis* is diagnosed at the very onset of symptoms and when such symptoms are slight, conservative treatment with light therapy has on rare occasions prevented the need of surgical intervention. As a rule **nephrectomy** is indicated. For unilateral progressive renal tuberculosis or bilateral disease in which the more involved kidney is removed, light therapy is to be advised as desirable postoperative treatment. It may have a favorable action on the genital organs and the remaining kidney and effectively contribute to the healing of tuberculous cystitis, whether alone or in association with medical treatment. Light therapy exercises a healing action on the stump of the ureter, which so often shows residual ulceration, resulting in a discharging sinus or a persistent cystitis. It has given excellent results,

even with chronic gaping wounds, extensive and deep, and even when covered with ulcerations and tuberculous granulations.

Light is particularly indicated in those not infrequent cases of renal tuberculosis complicated by genital tuberculosis in which the seminal vesicles and prostate are involved, thus often obliging postponement of cystoscopy to avoid trauma of the prostate and the risks of general infection. Therefore, before surgical intervention it is advisable to treat the concomitant lesions with a methodical course of light therapy to make cystoscopy and nephrectomy procedures entailing less risk of dissemination. In bilateral renal tuberculosis, light therapy is indicated. It may help render the disease quiescent; its occasional analgesic action on ulcerations of the bladder is particularly welcome. Advanced bilateral renal and bladder tuberculosis has rarely responded to any form of therapy, especially when the patient is cachectic. Postoperative sinuses, especially following nephrectomy, have responded in a large number of cases to light therapy of all forms. Local exposure to ultraviolet rays of circumscribed tuberculous lesions of the urinary bladder has been shown to yield favorable results, but the method requires special applicating devices and, above all, skilful treatment of the bladder lesion.

Lymph Nodes—Tuberculous lymph nodes in the stage of hyperplasia generally heal under solar and artificial light therapy. Occasionally they caseate under light treatment and surgical excision may be indicated followed by postoperative light therapy. Caseous nodes respond, although less constantly. Laqueified nodes require aspiration followed by light exposures. Sinuses from draining nodes indicate a course of light treatment. General and local irradiation are essential

over periods of many months. Not infrequently roentgen-ray exposures may have to be combined. At times, incision into a softening node is necessary.

Intestinal Tuberculosis — Granet and Ornstein³ state that the successful treatment of intestinal tuberculosis depends primarily on one key factor, namely, inactivation of the source of infection in the lungs. Absorption of toxins from active lung lesions by their noxious systemic effect prevents healing of intestinal lesions. Furthermore, the intestinal mucosa is constantly being reinfected with tubercle bacilli swallowed in the sputum expectorated from active parenchymal foci. While these factors are present, it is useless to expect permanent cure in the secondary intestinal lesions.

The treatment of the intestinal lesions must be undertaken simultaneously, and the measures used are twofold—general and specific. The general measures undertaken to improve nutrition, help tissue repair, and strengthen immunity. These include *actinotherapy*, a *high caloric, low roughage diet*, the administration of *vitamins C and D*, *iron* for secondary anemia, *calcium salts*, and, where indicated, *insulin* to stimulate appetite.

Specific local treatment is directed primarily toward fostering peristaltic rest in the involved segments of the intestine. Treatment depends on individual symptomatology, and must be changed frequently to suit the clinical course of the case. A smooth, low residue, high caloric diet, to which is added tomato juice and cod liver oil, is the standard dietary of these authors. Such a diet reduces peristaltic action to a minimum and provides an excess of vitamins C and D, shown to be of value in the metabolizing of calcium and the stimulation of mucosal healing. Abdominal pain is controlled by *heat* or adequate *sedatives*. Constipa-

tion is helped by small amounts of *mineral oil* or by gently administered *warm saline enemas*. Diarrhea is controlled by administration of *barium sulfate* or *kaolin* in half-ounce doses administered frequently and, if necessary, *tinctura opii deodorata* in effective doses.

Bellinger⁴ states that he has used ultraviolet energy and special diet since 1923, when they first instituted the program of control of intestinal tuberculosis as recommended by Brown and Sampson. The ultraviolet is supplied by mercury quartz burners supplemented by natural sun in the morning or evening hours of the summertime in suitable cases. The plan of gradually increasing the time and area in ultraviolet exposure has been followed from the start. Treatments are given daily except in tapering off what seems to be a successful course. Their principle is to thoroughly expose the skin area to mild exposures, or more intensive exposures, if well borne. In the earlier years, carbon arc lamps of various types were used to some extent and apparently good results were secured. However, mechanical objections of various kinds caused them to discard carbon arc lamps so that mercury quartz burners have been used almost exclusively during the past 7 years in the mechanical generation of ultraviolet energy.

The author believes that ultraviolet has been the most fundamentally valuable form of treatment in the work with intestinal tuberculosis. They have made it a practice to protect the eyes and head region. The chest has been protected to varying degrees according to the judgment of the various physicians. It is the author's personal belief that no one has proved ultraviolet to be especially injurious in the sense of causing new spread of disease or destructive changes

in tuberculous lesions and that, if we keep in mind the principle of mild exposures which can be given with comfort to the patient, the chest area can be exposed much more than it has been in the past. The reaction of the skin and comfort of the individual patient should be used as a guide. Skin irritation should be avoided as much as possible. Those with very sensitive skins may be hardened in by air baths and the air baths may be supplemented by the weaker ultraviolet lamps often recommended as "health lamps," but these should not be depended upon for definite treatment. On the other hand, intensive ultraviolet exposures crowded into the shortest possible space of time are neither necessary nor desirable. Rapid tanning should not be sought. Moderate doses will allow a gradual tanning without irritation or discomfort in those who respond especially well, and such doses should be our standard.

They have not tried roentgen-ray in treatment, though the author feels that they might have done better in some of their refractory cases had they done so. Very early in the diet they began allowing the use of some of the less fibrous vegetables and some of the fruit juices which were at first excluded. In their work they have found a plan based on the work of Grant, McConkey, *et al.*, essentially sound and they believe that the physician in general practice should see that the diet of his cases of tuberculosis and particularly those with possible intestinal involvement includes an *adequate supply of vitamins*. More specifically he should see that the supply of vitamins "C" and "D" are adequate. Tuberculosis apparently absorbs vitamin "C" in direct proportion to clinical activity. *Calcium* intravenously was started in their service immediately after the publication of the work done at the

Fitzsimmons Hospital in Denver, and calcium has been continued quite routinely in some form since that time.

Pelvic Tuberculosis—King⁵ states inasmuch as pelvic tuberculosis is known to constitute from 5 to 8 per cent of all cases of pelvic inflammation, its importance to the gynecologist is obvious. The preoperative diagnosis of tubal tuberculosis has always been recognized as being extremely difficult and, in many instances, impossible. It is unfortunate that diagnosis of early involvement of the tubes cannot be made, for King believes that early recourse to the accepted present-day treatment of pulmonary tuberculosis would heal the early tubal lesions equally well.

The first essential necessary in making a diagnosis of pelvic tuberculosis is for the surgeon, when dealing with pelvic infection, always to keep in mind that pelvic tuberculosis can and does occur. In any case in which the cause of the inflammation is not determined with reasonable certainty, the surgeon should be suspicious of tuberculosis. With this suspicion in mind, he is better able to elicit facts in the history and to undertake studies that may prove to be of distinct value in suggesting the diagnosis of tubal tuberculosis. King has often found that had a more careful inquiry been made into the past history of the patient rather than focusing too closely upon the pelvic symptoms, much that would have been suggestive might have been learned. The history of previous pulmonary infection or a possible pleuritis is of great importance; the association with one who has tuberculosis, and finally coughs and colds, may all be significant. A careful chest examination should always be made and, in the absence of physical findings, x-ray plates, read by an expert in their interpretation, should be resorted to. Here it must be

remembered, however, that a patient with chest signs may well have a gonorrheal salpingitis, and that one with evidence of gonorrheal endocervicitis may have a tuberculous salpingitis.

King is convinced that no patient should be operated upon in the presence of fairly well-marked pulmonary involvement. This is not so much because of any objections connected with surgery itself, but because in such cases the pelvic pathology is the less serious of the patient's infections. Radical surgery is seldom required. King is firmly convinced that every case of pelvic tuberculosis, regardless of how successful surgery may have been, should be followed by *sanitarium treatment* with heliotherapy. He states: "It is surprising how casually this most important part of the treatment is mentioned, if mentioned at all, by those who discuss treatment. This feature is most essential, and should always be strongly emphasized. It is unfortunate that sanitarium treatment consumes so much time, but at present there is no substitute. Following operation, the patient should be moved as promptly as possible to such an institution. The general condition of the patient will improve rapidly. A sinus, if present, will heal. What is still more important, it is the only means of healing the primary focus that has supplied the bacilli. For this latter reason, if for no other, such treatment is imperative."

Tuberculosis in Infants — Price⁶ states that differences of opinion exist regarding the prognosis of tuberculosis occurring in infants during the first year of life. Many authorities consider that there can be no recovery if the disease is contracted during this early age period. Others hold that recovery is rare.

Tuberculosis as it occurs in the infant is a special study, and differences between infantile, childhood, and adult

types must be emphasized. The infant gets its infection from contact with a human being in close touch with it, usually the mother; in this case the infection is repeated and often massive. Abdominal tuberculosis is rare in the first year of life; when it occurs it is as often due to ingestion of dried tubercle bacilli from floor dust as to infected milk. The main condition, therefore, which we have to deal with is inhalation infection with primary involvement of the lung. The infant shows little resistance to tuberculous infection, partly because it cannot get away from the source and so have time to acquire immunity, and partly because its defense capabilities in general are low during these early months of life.

Price states that first and mainly treatment consists in removal of infants from all possible tuberculous contact. They should not be put in sanatoria where there are cases of open phthisis. They should be taken to infant hospitals or preventoria, and the isolation must be maintained until healing is evidenced by calcification or by fibrosis. Calcification is the less usual end result because if infants have caseating foci there is nearly always a fatal termination. Fibrosis is the commoner end result, and here, in later radiographs, nothing abnormal is seen, and the only proof of past infection is the serial radiographs and a positive tuberculin test. Healing is established in mild cases in 6 months, but other cases may take up to 2 years. The falling of the sedimentation rate to normal also indicates healing.

The second essential of treatment is rest in bed. Movements in the cot have to be permitted, but exercise out of the cot must be postponed until serial radiographs and normal sedimentation rate and weight gain show that the lung is healed. Fresh air is essential throughout

treatment, but infants must not be exposed beyond their limits of endurance, and throughout the treatment they must be kept warm. Digestive disturbances must be attended to and a suitable diet rich in vitamins, with added calcium, must be given. Ultraviolet rays and strong sunshine are absolutely contraindicated in all pulmonary lesions in infants and children; however, in these climates outdoor shade in summer and exposure to sun in spring and autumn are safe. Temperature charts, the sedimentation rate, and radiographs all demonstrate how dangerous is sun bathing to a small child with a pulmonary lesion, be this only in the primary stage. It will be found that casualties occurring during the primary stage of pulmonary tuberculosis will be among those infants whose parents are not convinced, and who do not allow this treatment to be carried on until complete healing has been ensured.

Rickets

Luce-Clausen⁷ in considering the clinical aspects of ultraviolet radiation states that rickets is a disease caused primarily by lack of sunlight, it is a disease of sunless areas of winter months, a disease caused by artificial conditions which exclude sunlight. The curative effect of ultraviolet radiation on rickets and its prophylactic use in the prevention of the disease are based on known physiologic facts. Diets constituted in such a way that the ratio of calcium to phosphorus is high, usually about 4:1, and also deficient vitamin D, will produce severe rickets in rats, young rats, placed on such a diet, will survive the diet only from 6 to 7 weeks, and at autopsy will show all the classic signs of severe rickets. A short daily exposure to ultraviolet rays will, in spite of the deficiencies in the diet, make these rats survive

as long as 25 weeks. They may die, but with normal bones. The mechanism that makes an organism capable of supplying mineral constituents for bone formation, even in spite of a shortage of it in the diet, is set in motion by ultraviolet radiation.

In the solar spectrum the protective region is a very narrow band of radiation ranging from 296 to 310 millimicrons and furthermore these radiations must be present in sufficient intensity to produce their effect. Artificial sources of light, such as the carbon arc or the mercury vapor quartz lamp, emit radiations of shorter wave length than those found in the solar spectrum. Some of these—the region about 280 m μ —are markedly antirachitic; others around 248 and 240 m μ are less so. Many writers have investigated the depth to which ultraviolet rays penetrate the skin. Most of them are agreed that the penetration is slight, roughly only 0.1 mm.

Mode of Action of Ultraviolet Radiation—The author in considering the mode of action of ultraviolet radiation states that to understand how radiation brings about its effect in the cure of rickets one must have in mind 2 well-known facts. First, that in the development of the disease there is the local phenomenon of failure or delay in calcification taking place at the epiphyses of bone, and, second, that there is the systemic one shown by a chemical change in the blood resulting in a diminution of the concentration of phosphate. Rickets, then, is something more than a disease localized in bone, it is regarded as a general metabolic disorder.

Ultraviolet radiation raises the phosphate concentration in the blood and also promotes the deposition of lime salts in bone, through the agency of vitamin D which is synthesized in the skin. It is assumed that vitamin D, formed

in the skin, is absorbed into the blood stream and carried to the bones. According to the author this theory is supported by the work of Hume, Lucas and Smith, who showed that vitamin D could be absorbed through shaven areas of skin in rabbits, and more recently Lucas in a series of ingenious *in vitro* experiments has shown that sufficient ultraviolet of suitable wave lengths can penetrate the epidermis. It therefore might activate provitamin D contained in the subepidermal capillaries. The mechanism whereby lime salts are actually laid down in the epiphyses is not clearly understood. There is a vast and complicated literature on this subject but the *modus operandi* is still obscure. The author states that Robinson, in a series of important papers on calcification *in vitro*, has demonstrated the presence in the epiphyses of bone and in other tissues of phosphatase, a bone enzyme.

The part played by this enzyme and vitamin D in the absence of calcification when rickets is present, or in the production of calcification during its cure, is still uncertain. It would seem, however, that the concentration of phosphate in the blood is the factor that controls the deposition of lime salts, for, clinically speaking, it is unusual to detect healing in the bones by x-rays until a rise in blood phosphate has been obtained.

The seasonal variation in the intensity of the antirachitic rays of the sun is of the utmost importance when one considers sunlight as a therapeutic agent. Studies of the seasonal incidence of rickets have shown very clearly that the peak of cases occurs during the winter months when the ultraviolet of sunlight is of lowest intensity; the converse is also true—the fewest number of cases occur in the summer months, and summer is the time when spontaneous healing is observed. According to Luce-Clau-

sen,⁷ Hess and Lundagen demonstrated a seasonal tide of phosphates in the blood of infants in New York City which was shown very clearly to be a winter ebb and a summer flow. This occurred in spite of the fact that the infants were exposed to sunlight every fine day. In most of the infants some degree of rickets developed during the winter months in spite of excellent hygienic conditions. Hess regards a winter reduction of blood phosphate to be usual for infants living in the temperate zone.

Treatment—The author states that the treatment of rickets with ultraviolet radiation is much to be recommended, since ultraviolet radiation is a potent and reliable specific in this disease. The radiations may be either those of sunlight or those obtained from artificial sources.

The difficulty of using heliotherapy in the climate of the northern part of the United States during the winter is obvious from the preceding paragraph; the specific radiations are not available in sufficient intensity at a time when they are most needed, and, furthermore, the cold makes it difficult to expose much of the body surface to the direct action of the rays. Cold also makes it difficult to expose infants, however warmly clad, for a sufficient length of time. Hess found the curative use of heliotherapy unsatisfactory during the entire months of January and February and the early part of March in New York City. It is clear from this that, during the winter, treatment should be given from artificial sources.

In using artificial sources of radiation it must of course be remembered that radiations are present of far shorter wave lengths than those emitted by the solar spectrum, and also that the antirachitic solar radiations, in these lamps, form a much higher percentage of the total rays. A rough estimate of the anti-

rachitic radiations in sunlight in mid-summer is 1.5 per cent of the total energy, while many artificial sources emit these rays in amounts as high as 20 per cent. The lamps most commonly used are the air-cooled mercury vapor and the carbon arc. The former emits far more of the short wave-length radiation than sunlight; the latter approximates more nearly in distribution to the radiations of sunlight but still transmits a much higher percentage of these rays. Dosage with these lamps is still highly empirical, but in general the dosage should induce a slight, but avoid a marked, erythema.

Tetany

Luce-Clausen⁷ states that idiopathic tetany of infancy, the symptoms of which are well known, has an intimate relationship to rickets. The blood chemistry in rickets shows a diminution in the concentration of phosphates in the serum. In tetany the phosphate concentration of serum remains unchanged and may even rise, but the level of calcium in the serum drops from the normal of 9 to 11 mg. per 100 cc to 7 or 8 mg. in latent cases, and in cases presenting manifest symptoms it may be lower than this.

Ultraviolet radiation, cod-liver oil and activated ergosterol are just as specific and effective in the cure of tetany as they are in rickets. It has been found, however, in certain cases, that symptoms of tetany may be intensified at the outset of treatment. This is thought to be due to a sudden rise of blood phosphate caused by the treatment taking place before the level of calcium in the serum has risen. In this connection Hess and Lundagen, in discussing the seasonal tide of phosphates in the blood of infants, incline to the view that the increase in the concentration of blood phosphate which occurs in April and May may be

a contributing factor to the development of tetany in the late spring.

Ultraviolet therapy in tetany is of the utmost value. According to Luce-Clausen,⁷ Hess recommends its use as a prophylactic against tetany for all premature infants, as well as its use as a specific cure once the disease has occurred. Treatment is carried out in the same way as that outlined for rickets. It may be advisable to give doses of feeble intensity at first until the level of calcium in the serum rises and this should be combined with calcium therapy.

Dermatology

Luce-Clausen⁷ in considering the use of ultraviolet radiation in the treatment of skin diseases states that from experimental knowledge it would seem that the various effects of radiation on the skin must be brought about mainly in three ways:

1. A direct bactericidal action of the rays on organisms in the skin which lie within the depth to which the rays penetrate. This, as explained elsewhere, is a superficial layer, so it seems clear that organisms, if they are to be killed by the direct action of radiation, must lie superficially. The well-known beneficial effects of the Finsen treatment for lupus are probably explained as due to a direct bactericidal effect of the radiations used. It is also probable that the good results recorded in the use of ultraviolet radiation in the treatment of erysipelas are due to the same cause. Ultraviolet radiation may kill bacteria outright or attenuate their virulence if the organisms are given a sublethal exposure. It is thought that the latter effect may account for seasonal variations in the virulence of certain diseases.

2. An effect due to hyperemia. Ultraviolet radiation produces an initial hyperemia of the skin, which may be of

value in certain diseases of obscure etiology and when no causative organism has been isolated, such as psoriasis.

3. A possible effect, at present not well understood, of substances synthesized in the skin under the action of radiation. With the exception of the production of tan and the synthesis of vitamin D, the photodynamic effects of radiation on the skin are not well understood. That certain skin diseases occur as a result of photosensitization seems well established, but how this condition is brought about is not known.

Scholtz⁵ states that on the basis of the known facts concerning the bactericidal action of ultraviolet radiation and its ability to penetrate the skin, it has been asserted by most authorities (Laurens, Coblenz, Kovacs) that the bactericidal effect cannot be utilized for the destruction of bacteria in the skin. In spite of these opinions many claims are made regarding the clinical value of this energy which obviously has been so poorly controlled, due in part to the heterogeneous quality of the emission source and the varying nature of the physiologic response. Scholtz investigated the depth at which the pathologic process is situated in the bacterial diseases of the skin. Considering the known physics of ultraviolet radiation, its penetrability of the skin, and the site of the pathologic process, it can be determined on a theoretic basis which diseases might prove accessible to the bactericidal rays. The author emphasizes that we are concerned only with the accessibility, and no other consideration at this time.

Furthermore, we are not here concerned with the bactericidal effects secondary to erythema produced by ultraviolet or heat waves or the effects secondary to the systemic resistance created by radiant energy, but are restricted to a study of the direct killing property of

the ultraviolet spectrum. It is this direct effect for which so many claims are made and whose use is so often erroneously invoked.

It should be kept in mind that a very definite quantitative relationship exists, and that therefore a very definite quantity of a given type of radiation must be delivered to the site of the bacteria, *i. e.*, the percentage transmission of the various ultraviolet bands through the layers of the skin. It must be pointed out that it is this factor mainly which determines the applicability of ultraviolet as a direct bactericidal agent.

The author classifies the bacterial diseases of the skin according to the depth of the pathologic process, and the theoretically available amount of bactericidal ultraviolet radiation is indicated.

In his conclusions Scholtz states that from the facts known concerning the physical nature of the bactericidal ultraviolet, the penetration of the skin by the bactericidal ultraviolet and the depth of the pathologic process in the bacterial disease of the skin it is concluded that there are a small number of bacterial diseases of the skin accessible to the bactericidal ultraviolet. It is pointed out that since the bactericidal mechanism is based on a definite physicochemical phenomenon which requires a minimum amount of energy of given voltage, it is yet to be shown that the required amount can be delivered to the site of the pathologic process without producing undesirable concomitant effects.

Acne Vulgaris—Stryker and Bloom⁹ state that the therapy of acne vulgaris has been characterized by waves of enthusiasm for one therapeutic procedure after another. X-rays and ultraviolet rays are the mechanical devices which have played an important rôle in therapy. Having reached the stage of realism, x-rays have proven themselves, when

competently administered, the most useful single agent in the treatment of this disease. It is their opinion that this position will continue to be maintained. Ultraviolet rays, in spite of their limitation, are important adjuvants to treatment.

In reviewing their discussion the authors state that of the acne problem there appears to be 6 important factors; namely: (a) There is a hereditary predisposition to acne, (b) there is hyperstimulation of the pilosebaceous apparatus probably brought about by some unknown substance which appears with puberty and gradually diminishes as age advances, (c) an excess of sebum occurs, (d) there is a bacterial invasion of the sebaceous follicle, (e) hyperkeratosis of the epidermis develops, and (f) there is an indication of a decreased activity of the reticuloendothelial system of the skin

From the foregoing facts and in the light of our present knowledge and experience there is no logical reason to attempt short cuts in treatment. The most satisfactory approach to rational therapy is based on the assumption that each case be treated individually. A quick cure in young patients, except when disfiguring scars may occur, is not essential. The relations of the patient and physician are enhanced if there is an understanding that the juvenile phase of the disease must be managed until a cure can be brought about. This presupposes that x-ray will be used sparingly or not at all until the eighteenth year

MASSAGE AND EXERCISES

Fractures

Murray¹⁰ believes that we have reached a point in fracture management where we must believe in addition that the frac-

ture and the pathology of the soft part demand equal attention in the immediate and early treatment of the case. The late pathologic changes of fibrosis in muscle and ligament with or without contraction, of thickening and loss of elasticity in mesotenon and paratenon, of fibrosis in and about tendons and nerves and of lymphatic and capillary obstruction are the end result of abnormal conditions developing immediately after fracture. They represent in clinical terms the pain and ache associated with or without movement, limitation of joint motion, loss of muscular power, and swelling of the part whether secondary to or independent of functional activity. These late symptoms are a fixed tissue phenomenon. At the time of fracture and for some time thereafter these fixed tissue changes are represented by tissue death due to hemorrhage, exudate and cellular infiltrations in the soft parts about the fracture. The normal mechanism for the removal of these pathologic elements is the circulation in its broader sense, which includes the lymphatic and tissue fluid movement of the part. A good pulse and the absence of venous engorgement are no criteria of the adequacy of this mechanism. Swelling, pain, induration, tenderness and heat are the criteria whereby to judge the efficiency of this circulatory mechanism, which depends far more on the minute circulation in capillaries, lymphatics and tissue spaces than it does on the motion of the blood through the veins and arteries.

According to Murray, in addition to this conception of the place of soft part pathology in reference to both the speed and extent of functional return in the extremity, it may be accepted as an adequately supported principle that the healing of the fracture itself is in general dependent upon purely local factors. These local factors are concerned in the

production of the new and healing tissue, in the making available of calcium from the site of fracture for the ossification of that healing tissue, and in the mechanism of that ossification.

All other factors being equal, the decalcification of injured bone and the deposition of that calcium in newly formed fibroblastic tissue to form callus is dependent upon the pH of the tissue fluids in the immediate vicinity. Local low tissue fluid pH (acidity) is experimentally and clinically associated with decalcification of bone. Calcium deposition is associated with a high tissue fluid pH (relative alkalinity). It is a fact that the products of tissue death, local tissue fluid stagnation (inefficient lymphatic circulation), local blood vascular stagnation (congestion), and the products of the breaking down of hemorrhage and exudate all lead to and intensify a low pH of the tissue fluids.

So long as this acid phase of the reaction persists, decalcification of bone at the fracture site is the only process possible. There is much evidence to support the view that for the deposition of calcium the participation of an enzyme—one of the phosphatases—is necessary. It has been definitely shown that this enzyme is relatively or completely inactive in an acid medium, and cannot become active until a return toward the normal or even beyond normal pH levels in the local tissue fluids is attained. This can be accomplished at present only by the removal of the factors which result in acidity—a problem of tissue fluid, lymphatic and blood vascular circulatory efficiency.

The potentialities of early physical therapy as a factor in promoting the process of callous formation, assuming that proper physical therapy will increase the efficiency of this threefold circulatory mechanism, is obvious. Late physical

therapy holds no such promise. It then must deal with tissue already past the newly formed and differentiated fibroblastic stage, and new bone formation in such tissue; that is to say, long after the actively decalcifying phase which provides the calcium has subsided, and is slow and uncertain in production, even if possible.

To restore shoulder function following fractures of the upper end and shaft of the humerus, Gordon¹¹ has the patient bend forward with the injured arm hanging vertically to a point easily tolerated by the shoulder. Then with the muscles relaxed move the body so that the arm is set swinging as a pendulum, forward, backward, sideways, then in a circle with the clock and against the clock. This stretches the muscles. This is followed by making the same movements actively, slower than the pendulum time with the body at rest, which makes the shoulder muscles do work, *i e*, resisted motion in a position where gravity is overcome and which aids co-ordination.

Later, graduated weights can be held in the hand while doing these exercises. As function increases, the body is bent forward until the shoulder is performing at a point of marked upward extension of the arm. Gordon emphasizes to be sure that the movement takes place in the scapulohumeral joint and not in the scapulothoracic joint. The first has a protective reflex mechanism which splits against any pain by spasm. The latter has not this mechanism and most of the movement of an injured shoulder is scapular, until the surgeon and time correct this.

Where pain persists in the shoulder, hot stupes daily will give relief. For the loss of elbow function in shaft fractures, the above exercises are needed, to which is added resisted flexion, extension, pronation, and supination of the forearm.

"Climbing the wall" will be most commonly done with a fixed shoulder by means of scapular action which should not be done. It is only good to measure return of the shoulder function. With a high pulley through which a rope is passed with handles attached to the ends, the well hand can pull up the injured one for stretching the abductors, but do not have the injured one pull the good one up. The adductor muscles are already strong enough, contracted, and need stretching.

Practical fracture physical therapy should begin before the fracture is reduced and not after it has united, according to Wright.¹² He believes that there are many fractures which can receive simple physical therapy (gentle heat and massage) daily, after reduction. However, it can only be applied to those fractures which are capable of being treated by (and if the attending physician will adapt) "open types" of immobilization. "Out of sight, out of mind" is frequently the rule when a solid plaster cast is applied. Certainly it is "out of bounds" as far as applying physical therapy. When really necessary, casts should of course be applied, but the fact that many surgeons who are interested in fractures resort only infrequently to their use should demonstrate that they are not as often necessary as they are applied. The author believes that if the readers will preach and practice "open types of splinting" more often, they will enable their confreres, assistants and internes to practice early physical therapy because the injured parts will be accessible to early and better physical therapeutic measures.

Wright's method of treating a Colles' fracture demonstrates the above points. He reduces the fracture with or without anesthesia, by securing a firm handclasp grip of the injured hand and, while

firmly holding the lower forearm with the left hand, the surgeon—using traction with his right hand—quickly flexes and extends the fractured site 1 or 2 times, and "jerks" it into position. The hand is then placed in palmar flexion on a molded plaster-of-Paris, cock-down splint placed on the ventral aspect only, and running from just below the elbow down to the metacarpophalangeal joints. The latter length of splint leaves the fingers free for exercising. The wet, molded splint is made with a 1½-inch gauze bandage. At the end of 24 hours the splint is gently removed and 3 straps of 1-inch adhesive are substituted for the initial bandage used in applying the splint. The dressing is now an "open type" one, and the part is accessible to inspection, heat, and massage.

On his initial revisit Wright states that gentle massage is given and the patient is instructed to gently stroke the back of the hand and wrist for a period of 5 minutes, 3 or 4 times daily. The application of an electric pad (turned low) is recommended for half-hour intervals, 2 or 3 times daily. The patient is seen by the physician every 2 or 3 days in the early part of the treatment. On these visits the splint is gently removed, the hand kept in palmar flexion, and massage given to both aspects of the wrist and forearm. After 4 to 6 days, gentle passive flexion and extension are given to the wrist with gentle supination and pronation.

Wright encourages the patient to "practice piano playing" with the uncovered fingers at home. The splint is then discarded in from 10 to 20 days, depending upon the age and extent of the fracture. When the splint is discarded, a wrist sling is advised so the hand may be readily withdrawn for exercises and light tasks such as dressing, eating, combing the hair, etc. Directions

are then given regarding exercises such as squeezing a rubber ball or rubber sponge, or "newspaper exercise." In 5 weeks time, the average person may perform the majority of his daily tasks, unless he is engaged in manual labor. The patient is encouraged to use the hand as much as possible, up to the point of pain, and then to give it 5 to 10 minutes of rest. He is advised that the soreness (not pain) may be hurting him but that it is not hurting the bone and that the best way to get rid of soreness and stiffness is to "work it out." Wright states "After all, if it is difficult to reduce a 7-day-old fracture and impossible to reduce a 3-week-old fracture, even when the physician 'swings on it' under general anesthesia, how can the patient disturb the fracture site with less force?"

"This short period of immobilization may seem too little to some, but if they will test out the above method they will find that they will obtain earlier clinical union because of the improved circulation and physical condition of the fractured site and better condition of the associated soft tissues which, all too often, are forgotten. Remember always to treat the patient and not the x-ray film. There is always more callus present clinically than roentgenographically. Bear in mind 'clinical union' as your forefathers did."

According to Dickson¹³ there are 4 basic forms of physical therapy which may be employed in the treatment of fractures, they are heat, massage, exercise and muscle stimulation. The first 2 of these secure their effect by bringing about muscular and vascular relaxation; the third and fourth are of chief importance in promoting venous and lymphatic flow and preparing the muscles to resume their normal active rôle as soon as use may be safely permitted.

Heat may be applied in a number of ways, such as by a therapeutic lamp, diathermy, electric pad, and as radiant heat by the use of ordinary light bulbs set up in a cradle. Heat, to bring about the best results, should be employed at low intensity and over a considerable period.

Properly given, massage stimulates the nerve endings and activates sensory impulses of a wide variety which are important in relaxing muscular and vascular spasm and in relieving pain and discomfort. It also promotes the absorption of hemorrhage and an exudate by improving blood and lymphatic circulation in a damaged extremity. The type of massage most useful in the treatment of fractures is light stroking massage, the movement should be slow, even, steady and always in the same direction; that is, lengthwise of the part in the direction of venous circulation.

Muscle contractions may be produced by voluntary effort or by electrical stimulation. Voluntary contraction of muscle groups is incomparably superior to any form of artificial stimulation. Muscle stimulation by electrical stimulation, while not as satisfactory as active exercise, is nevertheless a useful therapeutic aid for maintaining muscle tone. To avoid painful contraction some form of sinusoidal current may be used. The Council on Physical Therapy of the American Medical Association will furnish a design for making a faradic sinusoidal coil. This coil produces a sinusoidal current which will give graduated muscular contraction as described by Bristow and Smart. The value of these contractions is primarily the increase in circulation in the muscle. When electrical stimulation is utilized to bring about muscle contraction, it should be painless and not cause muscle spasm; for, when pain and

spasm are produced, harm rather than good results,

Dickson¹³ believes that, practically, physical therapy can play but a minor rôle in the reduction period. However, when for any reason it is impossible to proceed with the immediate reduction of a fracture, even if the delay is but a few hours, heat and gentle massage may be used to advantage. When fractures are accompanied by severe trauma to the surrounding soft parts with extensive hemorrhage, and reduction, open or closed, must be delayed for several days, heat and massage may be used with considerable benefit to improve the condition of the soft parts and permit the application of definite treatment much sooner than would otherwise be possible.

In the postreduction period physical therapy should assume a very important rôle in fracture treatment, but, unfortunately, it is during this period that it is most neglected. It is quite true, Dickson states, that the application of physical therapy at this time is often difficult because the part is encased in a fixation dressing, but by the use in both bed and ambulatory cases of traction, which allows ready access to the part for physical therapy, through apertures in plaster dressings, by the use of hinged splints which allow movement in adjacent joints without disturbance of the fracture site, by the use of open splinting and by daily "setting" of the muscles, it is usually possible in most fractures to use heat, massage and muscle contraction throughout the period of fixation to the great advantage of the patient. So-called open splinting has in recent years been used more and more in the fixation of fractures, this permits the employment of physical therapy to a very satisfactory extent. By open splinting is meant using anterior or posterior or lateral molded plaster splints to replace

circular plaster dressings when possible; as, for example, in Colles' fractures, fracture of the patella and fractures of the ankle. Such splints afford ample exposure for physical therapy without disturbing the fracture.

It is in the period of aftercare that physical therapy is most generally used in fracture treatment. It is unfortunate that it is so frequently improperly used. The rôle of physical therapy in the after-treatment of fractures may be stated then to be helping the patient to regain voluntary use of the muscles and voluntary control of impaired joints of the injured extremity. Heat, massage and muscle stimulation can reduce swelling, can decrease pain, soreness and stiffness in weak and degenerated muscles, can improve vascular and lymphatic circulation, can stimulate neuromuscular and neurovascular impulses, can in brief make it easier for the patient to use the impaired part and build up voluntary control, but they cannot make him well. *The patient, in the last analysis, is master of his fate, and physical therapy is but the tool which enables him to carve out his recovery with the least discomfort, the greatest speed and to the fullest extent.*

The movements which are used should be designed to bring about normal action of the joint in the most natural manner. Having the patient go through the motions of brushing the hair in elbow fractures, driving nails with a light hammer in fractures of the wrist, turning a door handle in fractures of the forearm, and reaching for objects placed at a gradually increased height in shoulder fractures illustrate the methods which may be used to encourage the patient to use the extremity in a normal manner.

Chronic Arthritis

Key and his coworkers¹⁴ in the treatment of patients with degenerative arthri-

tis attempt to treat the joints in an effort to relieve the symptoms of which the patient complains and they also attempt to treat the patient as a whole in an effort to correct the abnormal physiology of the individual and to combat what they believe to be the underlying cause of the disease in each particular patient. In beginning the treatment of one of these patients it is advisable to explain to him the fact that, while he has chronic arthritis, he does not have the crippling form of the disease and is not on the road to chronic invalidism. He is then told that under proper treatment not only can it be expected that the joint symptoms will lessen or disappear entirely, but that if he will continue to follow out a given regime it is probable that the joint symptoms will not recur or spread to other joints and that he may be able to be more active without causing flare-ups of the arthritis.

In regard to the joints themselves, these authors believe that it is important to remember that a joint affected with degenerative arthritis is a worn-out joint and that further wear and tear is not a desirable method of correcting the condition. Consequently, when these patients have pain in a given joint it is advisable to rest this joint as much as is practical. This does not mean putting the patient to bed, except in very severe cases, but the patient with knees which are swollen and tender should avoid walking more than is necessary until the symptoms are better.

The knees should also be protected by elastic knee caps, stockinet, or other woven elastic bandages which both give support and prevent undue use. If the mechanics of the lower extremities are poor, the shoes may be altered and thus support the feet and lessen the strain on the knee joints, and, finally, the muscles of the patient may be built up

by exercises to such a degree that they afford added protection to the joints. These exercises can be taken by the patient while lying down and thus avoid the extra use which would result from similar exercises taken while the patient is standing. For the pain, heat usually is welcome to the patient and may be prescribed as baking or as hot compresses or in the form of diathermy. It is further advisable that the patients avoid exposure to cold—not only that they sleep warm, but for the fingers they are advised to wear woolen gloves and, in certain instances, woolen knee caps for the knees and woolen shoulder caps for the shoulders, as these joints do better if they are protected from the cold. In certain instances the patient is advised to soak the hands in hot water 2 or 3 times daily or he is advised to take contrast baths, putting the hands in cold water for 2 minutes and then in hot water for 1 minute, this is to be done for 30 minutes twice a day in an effort to stimulate the circulation. If the back is at fault it can be supported with a corset, a lumbosacral belt or a low back brace, and postural exercises are advised.

In the treatment of the patient as a whole Key and his coworkers¹⁴ prescribe a high vitamin, low fat diet for all these patients. If the patient is underweight the diet is high in calories and an effort is made to bring the patient's weight up to what we believe is normal for the given individual, if the patient is overweight, and this is the rule, a low caloric diet is given and an effort is made to bring his weight down to what we consider normal for the given individual. Routinely they add vitamins to the diets of the patients with degenerative arthritis, and they have not noted that vitamins A, C or D have any relation to the disease.

Underwater Treatment—For the underwater treatment of arthritis, Currence¹⁵ has devised a modification and several improvements of the original Hubbard tank. The design has been altered so that both ends are oval shaped with all corners rounded. It permits the technician to reach the axilla of the patient on either side without entering the tank. The patient is enabled to relax with his head on an adjustable built-in headrest. The tank provides complete range of motion of all joints of the body. It has sufficient inlets and outlets to facilitate complete filling or emptying with the water at any desired temperature, in less than 5 minutes. Two electrically driven turbines mounted in the tank produce an efficient form of gentle massage which can be applied directly to the affected part. A thermostatic water mixing valve of sufficient capacity, with volume control, provides for rapid temperature changes which are accurately indicated on a dial thermometer. Patients incapacitated and not able to enter the tank unaided may be swung on a stretcher supported from an overhead carrier and lowered securely into the tank.

The patients are usually placed in the tank in comfortably warm water, approximately at 100° F (37.8° C). After 3 to 5 minutes the temperature is gradually increased to 104° to 106° F. (40° to 41.1° C) until they show a rise of about 1° F in body temperature, when the water temperature is rapidly reduced so that no further rise in body temperature occurs. This is followed by several gentle passive movements of the affected joints without producing acute pain, as a single forced movement of a joint is likely to produce an exacerbation. With patients who are not hospitalized the temperature of the water should be cooled until the body temperature is

one-half degree lower than that in the beginning to avoid catching cold; but if they are to be returned directly to bed, they should be covered with several blankets and allowed a period of about 1 hour to gradually cool off prior to receiving an alcohol rub. If no reaction occurs from this treatment within 24 hours, another should be given which should increase the oral temperature a total of 2° F. Again reactions must be observed, and treatments continued until oral temperatures of 101° to 102° F. (38.3° to 39° C.) are attained. Two or 3 treatments weekly are administered according to the strength of the individual, usually in courses of 4 to 6 weeks, and resuming after a rest period of 1 to 2 weeks.

If a reaction should occur from the initial treatment, the patient should be kept at rest for at least 24 hours after the reaction has completely subsided before another treatment is given, and the dosage should not be increased until no further reaction occurs. Then the same procedure should be followed, using gradually increasing doses.

General Treatment—Myers¹⁶ in discussing the treatment of rheumatoid arthritis emphasizes the place of physical therapy in the program of treatment. He mentions the following factors in treatment: (a) Foci of infection; (b) abnormalities of colon function, (c) malnutrition, (d) anemia, (e) factors of metabolism, (f) deformities and limitation of function of the joints and periarticular structures, (g) mechanical defects in the function of joints, and (h) the mental state of the patient. He believes that rest is of utmost importance, probably the most important single factor in the treatment. Rest in bed, however, is not sufficient. Too often one tells the patient how many hours to spend in bed without regard to worry,

anxiety, restlessness and tension. By rest is implied relaxation, repose and avoidance of fatigue.

Myers states that co-operation from practitioners of various specialties is essential for the care of the arthritic. Particularly is this true of the internist, orthopedist and physiotherapist. Too often the internist and the orthopedist discount the value of the other's services. The one is inclined to apply his knowledge of the other's field. Too often the orthopedic training of the internist is rather elementary and the orthopedist's approach to the problems of internal medicine is superficial. To the internist the orthopedic problems of correction of existing deformities are difficult of solution. Even more important are the knowledge and equipment for the prevention of joint deformities, inadequate care for even a few weeks may permit the development of distressing deformities. The prescribing of physiotherapeutic measures means a great deal more than sending the patient to a physiotherapy technician. Detailed directions are to be given as to the measures to be employed. The patient with rheumatoid arthritis must have his directions for rest tempered with exercise. This may be general exercise, such as walking. Frequently indicated are postural exercises, muscle-setting exercises, and the retraining of groups of muscles which have become atrophied from disuse. In some instances passive exercises, such as massage and passive movements of the joints, are advisable. The various measures for increasing heat locally, such as baking, diathermy and the like, are helpful in the relief of pain and probably of the inflammatory process.

Treatment of Chronic Atrophic Arthritis—Thompson, Wyatt and Hicks¹⁷ discuss the treatment of chronic atrophic arthritis. This terminology is

synonymous with Type 1, chronic infectious, chronic proliferative, chronic rheumatoid arthritis and arthritis deformans. Their group of patients has received a composite treatment as indicated in the table. The authors wish to emphasize that no single treatment is specific in this group. An ideal treatment plan embraces a composite program directed to the amelioration of the manifestations of a symptomatic and constitutional disease.

I Prophylactic

A Removal or Correction of

- 1 Infectious factors—early treatment or removal of focal infections before symptoms appear
- 2 External factors—avoidance of chilling, damp climates, trauma, etc
- 3 Constitutional factors—proper attention to constitutional inadequacy—conversion of the "arthritic soil" into a "nonarthritic soil" by detailed attention and treatment

II Active

A Constitutional

- 1 Treatment or removal of focal infections
- 2 Rest
- 3 Physical Therapy
- 4 Diet
- 5 Transfusions
- 6 Heliotherapy
- 7 Climatotherapy

B Local Prevention of Deformities

- 1 Rest to inflamed joints, either bed rest or by proper orthopedic appliances or both
- 2 Motion—early through painless range to prevent ankylosis, later active exercise to restore muscle tone

C Correction of Existing Deformities

- 1 Nonoperative
 - (a) Traction
 - (b) Cast wedging
 - (c) Turnbuckle and other adjustable splints
 - (d) Manipulation
 - (1) With anesthesia
 - (2) Without anesthesia

2. Operative:
 - (a) Arthroplasty.
 - (b) Capsuloplasty.
 - (c) Tendon lengthening or shortening.
 - (d) Osteotomy.
 - (e) Synovectomy.
 - (f) Arthrodesis, etc
- D. Antigens and Vaccines
- E. Drugs:
 1. Nontoxic:
 - (a) Salicylates
 - (b) Iron.
 - (c) Rarely opiates (caution).
 - 2 Toxic or of doubtful value
 - (a) Gold salts
 - (b) Sulfur
 - (c) Chaulmoogra oil
 - (d) Arsenicals
 - (e) Cinchophen and derivatives
 - (f) Massive dose of vitamin products
 - (g) Colchicine
 - (h) Snake venom, bee sting extracts, etc

Rest, both general and local, is necessary in the treatment of this disease. Nearly all these patients complain of early fatigue. The patients were instructed as to the proper amount of rest during each 24 hours. Activity must be kept within the limits of fatigue. The amount of bed rest is variable. In cases with hot, swollen, weight-bearing joints the bed rest should be absolute until the inflammation has subsided. This may be a period of weeks or months. The joints are carried through a painless range of motion several times daily. These rest periods are always carried out with the joints in the position of extension and function and maintained in that position by necessary appliances. Later, graduated activity and exercise may be permitted. There is no treatment directed to the joints as valuable as rest. With it the inflamed joints are kept motionless and the weight bearing and movement trauma entirely eliminated. It is often surprising how well

these mentally and physically fatigued patients respond to bed rest. Naturally in some cases only minimal rest is desirable.

Nearly all these patients received **physical therapy**. This includes heat of all types, light massage, water, mechanical and electrical modalities and other physical agents. These valuable adjuncts to the treatment of atrophic arthritis will not be discussed as there is a wealth of available publications on this subject. The authors state that their staff includes 2 competent physiotherapists who work under direct medical supervision. With portable equipment it is possible to treat patients at home as well as at the clinic.

The authors have noted in this group little benefit derived from hyperpyrexia (induced by any means). They reserve its use to gonorrheal arthritis, where it is extremely valuable.

Nearly all arthritics of this type are benefitted by a **warm dry climate** such as there is in the Southwest. It constitutes a valuable aid in the treatment of those patients who can spend a sufficient time in such a climate. It is equally true that a few are not benefitted. **Heliotherapy** was used in the treatment of the majority of these patients. Sun bathing was prescribed at a regular time, with duration and amount of exposure definitely indicated. There are a few contraindications to direct heliotherapy, namely (a) The presence of fever; (b) the appearance of a general or local reaction, and (c) complicating or debilitating conditions such as active tuberculosis, chronic myocardial disease, general debilitation and old age, etc. In febrile patients it is wise to give no direct heliotherapy but to utilize the indirect type. In case of a general or local reaction it is well to minimize the time of exposure, eliminate it entirely or to

prescribe only indirect heliotherapy. The authors believe that both climate and sun are valuable agents in treatment.

Spastic Paralysis

In discussing the essentials of the treatment of spastic paralysis Girard¹⁸ believes that the primary objectives in the treatment of spastic paralysis are the prevention or correction of deformities and the teaching of relaxation and co-ordination. These objectives are obtained through physical therapy, occupational therapy, proper selection of toys and surgery. In all cases there will be periods when no appreciable progress will be noted, but neglect of treatment at this time may permit the development or recurrence of deformities. The progress, at best, will be extremely slow, but with patience and perseverance over a period of years, it is surprising, even in severe cases, how much improvement may be obtained. The training possibilities of the spastic child have no limits. The parent or instructor should never impress upon the child the feeling that his progress has been discouraging or disappointing, always avoid any sense of complete failure. This feeling certainly would not be conducive to putting forth one's best efforts.

Frequently it will be found that a spastic child may relax better upon a hard bed rather than on a table. Also, children frequently will co-operate better if the exercises are given with their clothes on instead of undressed. If a child tires of taking the exercises, he should not be forced to continue but should be given a short vacation or rest from the treatments, from 1 to 2 weeks.

Girard¹⁸ states that exercises in a warm swimming pool are good for certain cases, but, in general, pool work is too exciting and frequently causes increased rigidity of the muscles. If this

type exercise is used, the water should be warm and the child treated during a period when no other children are in the pool, and then only under the direction of a trained person. Under these conditions pool work is excellent. This form of treatment is practical and very useful in adequately equipped institutions.

The treatments range from the simpler to the more complicated. A certain child need not necessarily begin at the beginning but should start on that exercise which he is able to do easily and then work on through the more complicated ones. The arrangement of exercises should not be according to certain parts of the child's body but according to their simplicity and should be listed in the normal order in which they should be given. If only one part of the child's body is involved, only those exercises pertaining to that part should be given.

GIRARD'S OUTLINE OF TREATMENT

- 1 Physical therapy morning period 45 minutes
- 2 Rest hour 12:30 to 2:30 P. M.
- 3 Speech training 2:30 to 2:45 P. M.
- 4 Rest period 2:45 to 3:15 P. M.
- 5 Occupational therapy 3:15 to 4:00 P. M.

Physical therapy deals with exercises designed to teach the child voluntary relaxation and co-ordination. By this is meant teaching a child having a spastic or tight muscle group to relax that group voluntarily and then to contract the opposite group, not with all the power he possesses, but just enough to accomplish the desired motion in an easy, graceful way. This is not an easy task and requires endless endeavor on the part of both child and instructor. Grasping a spastic muscle gently, stroking or tapping frequently causes noticeable relaxation. This, then, becomes the simplest form of physical therapy. The

instructor or mother should not be in a hurry, under tension, or bothered with household duties when giving instruction. The same hour each day should be set aside for the treatment. The room must be quiet, warm and free from outside influences, such as other children and objects which distract the child's attention.

According to Phelps¹⁹ it can be said that throughout the entire treatment of cerebral palsies repetitive methods are of definite use for spasticity but are of no avail for athetosis, as, with the latter, attempts to carry out definite repeated activities in speech or in the use of the arms or legs are doomed to failure. This difficulty is carried over into the mental and general life, and repetitive methods have been found to be generally unsuccessful in all lines in the teaching of athetoid children. It can be seen that the training of such children is a general problem and involves the orthopedic, psychologic, speech and educational fields. The activities must be so inter-related that the therapist in each field knows clearly what is being carried out in the other fields.

Obviously, fundamentals must be stressed first, and in this instance fundamentals represent primary motor activities. No reliance must be placed on what are generally considered automatic instinctive activities. The young animal is able to walk if not on the day of birth at least within a few days, because of the automatic application of alternation in the legs in muscular contraction. However, if a part of the motor mechanism which controls alternation is interfered with, alternation will have to be taught as a voluntary function and trained into the habitual level before any attempt to alternate progression of the legs can be made.

In the athetoid child, the primary ability to move is undisturbed, since the damage does not lie in the pyramidal or voluntary motor system, but the activities are hampered by the superimposition of involuntary motion, which steers the voluntary attempts in the wrong directions.

Phelps¹⁹ states that the athetoid child reacts to his involuntary motion by voluntary tension, and after a number of years the tension habits become so fixed that he cannot make any motion without bringing in extreme stiffness. His habits must be unlearned in order to bring about a diminution of the athetosis. Athetosis disappears during sleep, and the amplitude of the involuntary motions decreases greatly with relaxation and increases with increased tension. Through the teaching of extreme relaxation the amplitude of the involuntary motions associated with athetosis can, in many cases, be so reduced as to be almost negligible. It is possible to teach relaxation by special methods to very young children and even to babies. It is, therefore, not necessary, for example, to teach a truly athetoid child alternation exercises of the legs.

Another phase of the problem which must be considered before a treatment unit is set up is the distribution of the involvement in the individual case. Is the child most in need of being taught to walk or are the problems of speech or of use of the arms more important? A great many children are seen who have been the rounds of many physicians and on whom a large amount of the time has been spent on operations and treatment for the legs although the arms and the speech are practically useless. When the legs and likewise the arms are useless, the question of future walking is much dependent on the development first of the proper use of the arms

Phelps¹⁹ states that the general care, therefore, of the spastic and of the athetoid patient and of the patient with any other type of cerebral palsy is rather complicated. There must be a program correlated by the orthopedist, the pediatrician, the neurologist, the physical therapist and the speech expert for the motor side and by teachers accustomed to handling the problems of the handicapped on the educational side, and psychologic aid is necessary in adjusting these children and their behavior to the world at large. Physical therapy in the primary stages of the condition should be followed by occupational therapy when the primary motions can be performed and grouped. This should give way to vocational training when the patient is old enough to determine the line in which he is to be trained. The program constitutes an effort to parallel the mental education of the normal child with a program for physical re-education which for the normal child is to a great extent automatic.

A great deal can be gained by starting treatment in these fields very early. The sooner the child is able to find out that a special regimen is necessary in order to make his body work for him, the less unteaching of bad habits of action will have to be utilized. During the preschool period, that is, between the ages of 2 and 5 years, the speech work should be begun. Phelps believes that it is useless to attempt to teach speech to babies under 1 year old. They learn gross motor co-ordination involving large joints, such as the hips, the shoulders and probably the elbows and knees, comparatively easily, but little should be done at this stage with regard to the fine co-ordinations, which are not normally developed in the child until the primary school age has been reached. In the preschool child, behavior is very im-

portant. It is necessary that he be much more responsive to disciplinary measures than the normal child, as the effort and the necessary obedience to make him carry out the corrective measures is important. It is during this age that walking should be started if it is to be attempted.

As the child becomes older the various activities become more skilled in type. For example, the child at the early primary school age spends a great deal of time playing games such as hide and seek and tag, which require little or no skill. After 2 or 3 years he attempts to roller skate or to skip rope, and a gross type of skill is developed. It is necessary to parallel this type of skill in the handicapped child who has reached that age. The idea of the optimal time for different types of activity should carry through the entire training period. The author emphasizes that types of skilled motion which are not learned by the normal child at a given age should not be taught the handicapped child before he has reached the age when he should acquire these skills naturally.

Infantile Paralysis

Ober²⁰ in an article for the Council on Physical Therapy emphasizes that the first stage, or the acute stage, lasts from the onset until muscle and nerve pain and tenderness disappear. It is during this time that the patient is very apt to be exquisitely tender in his legs, calves, thighs, hips, back and also in the adductor region of the shoulders. Patients who are very sensitive in these parts may assume protective positions of flexion in order to relieve pain and thereby develop deformities. To prevent such conditions occurring, properly covered and padded wire splints must be applied to hold the extremities in the position of comfort.

Ober states: "On no account should efforts be made to stretch out flexed limbs while they are tender. The use of hot packs or better still, if the patient can stand moving, a deep hot bath for a few minutes each day are the 2 best forms of heat to be used in relieving and relaxing the sensitive extremities. Dry heat in the form of lamps or diathermy has no advantage over these methods. No massage or exercises should be started during the stage of tenderness, since they do nothing but increase the pain and delay favorable progress. Absolute rest in bed and daily hot packs or hot baths at a temperature of 105° F. (40.5° C.) must be insisted on, since these are more effective than any other form of therapy. The patient will often move his extremities a little in the hot bath without detriment."

The second stage starts when all the signs of tenderness have disappeared. The author emphasizes that in this stage baking with electric light lamps and gentle massage promote the circulation in the muscles. These should be followed by active exercises on the affected muscle or group of muscles. If the muscles are too weak to function against gravity and friction, these should be removed. Exercises given in a pool or tank of warm water eliminate friction. It is very simple to construct a house tank of galvanized iron about 2 feet in depth, 4 feet in width, and 6½ feet in length. Ober²⁰ is of the opinion that early walking should be discouraged. For a moderately paralyzed patient whose morale is low, simple walking splints may be applied and the patient allowed to walk a little each day; but he should not be allowed to get fatigued. It must be remembered that walking does not increase the strength of the muscles. The third stage is usually represented by the end of maximum recovery of power

of muscles and has been arbitrarily placed at 2 years, and Ober states that it is during this stage that fixed deformities must be relieved by operative measures such as arthrodeses and tendon transplantations.

Hydrogymnastics—In a recent Public Health Bulletin the Kendalls²¹ give their views on underwater exercises. They believe definitely now that underwater exercise has no place in the early treatment of poliomyelitis patients. A functional gain at the expense of actual muscle power is a product of substitution and most detrimental in early poliomyelitis patients. Their reasons for this belief are: Protection is of primary importance at all times. If adequate protection in the form of noncorrodible braces for water use is applied, especially for a patient with extensive involvement, he is so encumbered that the value of the buoyancy of the water is lost. Relaxation of muscles is valuable in regard to contracted or spastic muscles, but not in regard to flaccid muscles. Relaxation does occur in warm water, and with exercise in the water the added relaxation creates a danger of stretching the weak muscles, especially if full range of motion is permitted.

Substituting the action of one group of muscles for another is much easier and is less apparent under water than outside the pool on a table. A very weak muscle will fatigue with only a few movements whether outside the pool or under water. The patient will not feel the fatigue under water because it is so easy for him to substitute other muscles in order to accomplish movements, and he will frequently continue to a point of far greater fatigue to his weak muscles than he realizes. The localization of exercise to weak muscles which is of utmost importance in order to build up a balanced musculature is very difficult

under water. With a patient supine on the table outside the pool, the entire body is fixed by the weight of the body on the table, as the operator treats one part at a time. With the buoyancy of the water it is almost impossible to fix adequately the entire body to insure such localization of exercise. If the principle of restricting the range of motion is observed there is little advantage in putting a new case in water. If it is not observed, it is in our opinion detrimental to permit stretching of the muscle through the full range of motion under water. The buoyancy of the water will relieve weight, thereby relieving strain, but will not prevent stretching of the muscles.

These authors, although they do not advocate the use of underwater treatment in early cases with marked weakness, feel it has a definite value in the treatment of poliomyelitis cases during later stages. If a child has recovered sufficiently so that the weight-bearing muscles have about 70 per cent of their normal power and are well balanced, walking in the water furnishes an excellent means of beginning activity without danger of strain.

Again, if an individual has considerable residual weakness after the first year in muscles which can be effectively braced, he may be greatly benefited by a generalized activity such as walking in the water, with the aid of lightweight water braces.

In old poliomyelitis cases, in which rest and protection have failed to prove of value in restoring actual muscle power, the patient may obtain much benefit from exercises of various forms in the water. Such activity is stimulating to the body in general, toning up systems other than the muscular, promoting normal function, and overcoming tendencies toward sluggishness.

Mills²² in an analysis of Sister Kenny's method of using physical therapy in the treatment of acute poliomyelitis states that the accepted or orthodox methods of treatment may be summarized as follows:

1. Rest and immobilization of the affected limbs until the stage of pain or irritation is past.

2. Maintenance of affected muscles in a position of relaxation

3. Avoidance of contractures and deformities by light retentive apparatus.

4. Massage and active and passive movements.

Treatment along these lines is based upon the theory that the pain in the limbs is of central or meningeal origin, and that rest and immobilization will remove the harmful afferent stimuli and enable reparative changes to take place in the cord. The stage of irritation or painful period lasts on an average 6 weeks and may be prolonged for 3 to 6 months. Immobilization and rest during the whole of this stage is not considered detrimental by many authorities.

In opposition to this accepted theory the view is taken that the pain in the extremities is almost completely vascular in origin. Some of the pain may be of central origin, but this takes the form of spontaneous or root pain and is not aggravated by movement. The vascular pain results from venous engorgement and consequent anoxia of the paralyzed muscles. The venous return from the extremities is influenced mainly by muscle tone and activity. In poliomyelitis the interference with this venous return is often of extreme degree. At first there is venous stasis, and later on capillary stasis and capillary paralysis; this is manifested by the coldness and cyanotic appearance of the limb and is accentuated by immobilization and splinting, especially in the position often adopted; that

is, abduction of the upper or lower limb. As a result mild trophic changes develop in the skin, bones, joints, fascia, and especially in the muscles. Immobilization of paralyzed limbs, with consequent vascular catastrophe, leads to contraction of the muscle sheath and anemia of muscle fibers, with subsequent mild fibrosis, seemingly a clinical entity, comparable to a very mild Volkmann's ischemic contracture. It has been demonstrated that complete obstruction to the venous return from a muscle leads in a few hours to profound muscle changes and is the causative factor in Volkmann's paralysis. A parallel may be drawn between the etiology of the 2 conditions. The importance of this ischemic pseudo-paralysis is recognized when it is understood that it renders muscle re-education extremely difficult. It is accentuated both by stretching and relaxation of muscles, as in the position of relaxation the muscle sheath contracts, tending to cause a permanent shortening of the length of the fibers and often resulting in slight deformities.

The irritation stage is an artificial stage which may invariably be overcome in 2 or 3 days by a well-regulated system of frequent passive movement, fomentation, and hydrotherapy. In no case does pain persist more than 3 days, although it usually will recur in the early mornings after the limb has been rested during the night. Cutaneous hyperesthesia also disappears under the treatment. As soon as the temperature drops, the active phase of re-education is started; that is, re-education is begun within 1 week of the onset of paralysis instead of after 6 or more weeks. In those cases in which a slight rise of temperature persists, treatment is carried out in spite of the pyrexia.

Massage has little part in the restoration of circulation, to which all efforts

must be directed. By massage the blood is merely squeezed from one set of dilated capillaries to another. Only some method by which capillary tone can be re-established is effective. Such a method is a system of hydrotherapy which makes use of the rapid alternation of hot and cold sprays in the bath. The limbs become suffused with a pink color within 10 minutes, the areas last to lose their cyanotic appearance being those which overlie the paralyzed muscle groups. By this simple measure applied daily trophic changes are avoided and the later application of such operative procedures as sympathetic ramisection rendered unnecessary.

Sister Kenny's methods have been in operation in the State of Queensland, Australia, for the last 16 years. Mills²² further states that instead of being dealt with by rest and immobilization in the acute stage, the affected limbs must be treated energetically, by fomentations, by hydrotherapy, and by movement through every range of each joint every 2 hours, and a finely graded system of re-education must be started as soon as possible, usually within the first week of paralytic manifestations. Under such a régime, wasting of paralyzed muscles occurs only to a small degree.

As soon as the temperature falls, the active phase of the treatment is begun and may be summarized thus: (a) The individual treatment of the patient and maintenance of a cheerful mental outlook, (b) special form of hydrotherapy, (c) maintenance of impulse; (d) avoidance of fatigue, and (e) avoidance of immobilization.

This active phase is instituted with extreme care, because it must be remembered that most of the residual anterior horn cells are still in a state of cloudy swelling. The patient must be treated alone because it is of major importance

that the whole attention should be concentrated on the treatment and not diverted elsewhere. Above all, an atmosphere of confidence must be maintained. The patients are placed upon a canvas sheet, lowered into the bath and given the form of hydrotherapy previously described. The joints are moved passively every 2 hours, and on only 1 occasion each day is an active attempt at movement of the affected muscles made. If a limb shows extensive paralysis, only 1 muscle group is exercised at a time, the other muscle groups being exercised at later intervals in the day. The active attempt at movement involves a special re-educative technic and is carried out as follows:

The limb is grasped firmly just below the insertion of the paralyzed muscle or muscle group, and the patient is asked to make the movement. Special grips are used to prevent accessory or trick movements. The patient focuses all his attention on the affected muscle and the attendant slowly performs the movement passively. Within a few days a trained assistant will detect a faint change in the affected muscle. It can be detected long before the finest movement is noticeable; it represents the first stage in the return of tone (subliminal excitation) in the muscle, and is termed "the impulse."

POSTURE AND BODY MECHANICS

Lenhard and Kendall²³ for the past few years have been much interested to find that the examination of patients with persistent sciatica gives a picture of muscle weakness, imbalance, and contracture that may help to explain the pain when the radiographs are negative, suggesting a diagnosis of chronic lumbosacral or sacroiliac strain. Almost without exception the patients with chronic

sciatica have a slight adduction and internal rotation of the affected hip. This may be associated with a tilt of the lumbar spine, although in a great many cases the lumbar spine appears straight. It is sometimes necessary to have the patient stand for a minute to tire the weak muscles sufficiently to demonstrate the asymmetry of the lower back and hips. One finds the posterior superior spine and the crest of the ilium slightly higher on the side of the sciatica. There is usually pronation of the feet, more on the affected side, and an increase in the normal lumbar lordosis. With the pelvis tilted forward and the thigh rotated internally, the fascia lata becomes contracted. If these findings be true, one can see that there is tension on the gluteal muscles, the abductors of the hip, the piriformis, which is an external rotator of the hip, and on the fascia lata that extends over the gluteus maximus. A weakness of the gluteus medius on the side of the sciatica can be demonstrated in all such cases. While the patient lies on the unaffected side with the lumbar spine straight, the affected leg is extended, abducted, slightly rotated externally and brought into slight hyperextension. When the leg is held in this position against resistance, the gluteus medius, an abductor of the hip, is found to be weaker than the gluteus medius of the other hip, when the corresponding test is done on that side.

Proceeding on the basis of these findings, the treatment used by Lenhard and Kendall²³ consists of relieving the pelvo-femoral muscles from tension, strengthening the weak gluteus medius, and by the usual methods of exercising postural balance to the lumbar spine. Radiant heat to the lumbar spine, massage and stretching of the lumbar muscles are followed by exercises for the abdominal muscles, gluteals, hamstrings and gluteus medius. By a lift, which may vary from

$\frac{1}{4}$ to $\frac{7}{8}$ of an inch, on the heel of the shoe of the unaffected leg, they are able to shift the pelvis and abduct the affected hip. By a slight elevation on the inner border of the heel and sole of the shoe of the affected leg they are able to rotate it externally. This elevation may vary from $\frac{1}{16}$ to $\frac{3}{16}$ of an inch. By exercise, the gluteus medius and abdominal muscles are strengthened in order to restore muscle strength and balance to the hip and lumbosacral areas. By the shoe lifts, they have been able to demonstrate immediate relief in some cases while the patient is standing during the period of the examination, and by the exercise program to establish relief that has been maintained. This outline of treatment apparently obtains relief for patients by releasing tension from the region of the buttock.

In considering the therapeutic value of postural correction, Nicholson and Laplace²⁴ state that most physicians think of postural correction chiefly as treatment of round shoulders and sway backs which are associated with a greater or lesser degree of kypholordosis of the dorsolumbar spine. The pain in such cases has its origin in fatigue of the muscles and strain on the ligaments which maintain the erect position of the vertebral column. The more pronounced the abnormal curvature of the spine, the greater becomes the mechanical disadvantage to which the supporting structures are subjected, so that the process is a vicious circle. In addition to fatigue and strain, there is involved also a secondary factor. Constant stretch causes small tears of the ligamentous attachments. This results in a series of subperiosteal hemorrhages with later calcification and the development of exostoses which may become extremely painful with additional strain and ligamentous tears. Arthritis of this type may occur

in any joint which is subject to prolonged strain, and is particularly common in the spine. Postural correction is indicated not only for the relief of symptoms but as a prophylactic against hypertrophic arthritis of the spine.

Less frequently recognized because it tends to simulate visceral diseases is the type of pain which was termed intercostal neuralgia by Carnett. It is caused by narrowing of the intervertebral foramina with consequent pressure upon nerve roots. In the cervical spine, especially in the presence of hypertrophic changes, the condition frequently gives pain referred about the shoulders and down the arms. This even in absence of circulatory disturbance has been mistaken for angina pectoris. The recognition of this pseudoangina and its cure by postural correction can save many individuals from a life of fear and invalidism. Similar neuralgic pains in the chest wall are often mistaken for pleurisy, pleural adhesions or pulmonary lesions. In the abdomen, narrowing of the intervertebral foramina may cause severe pain which has segmental distribution and can be evidenced in the skin, muscle or parietal peritoneum. It is usually misleading as to its origin, as it suggests the presence of some intra-abdominal disorder. A number of cases are recorded in which 2 or more surgical procedures were carried out before the true cause of the pain was determined.

The importance of body mechanics as a necessary part of preventive pediatrics is emphasized by Sweet²⁵. He believes that efficient use of the body has so evidently a favorable effect on the general health and well-being that it is accepted as an axiomatic point of departure by most writers on the subject. The bad effect of poor general health on body mechanics, with its attendant lack of muscle tone, lowered threshold of fatigue

and lessened available mechanical and emotional energy, is also evident. It seems unnecessary to argue that poor body mechanics and ill health form a truly vicious circle, each in turn increasing the other.

That pediatricians and other physicians are interested in the body mechanics of children is evident from the number who prescribe some form of corrective shoe for many of their patients. Every physician who cares for children should be interested in their feet. He should teach mothers that short socks and short, ill-fitting shoes may cause irreparable damage to growing, easily deformed feet; that children under 7 years of age rarely, if ever, complain of short shoes but walk with the feet everted and pronated to relieve their toes from pressure, thus forcing the feet to bear the weight of the body too far mesially on the inner borders of the heels and on the first metatarsal bone, while nature designed the feet to bear weight centrally on the heel and only slightly more on the first metatarsal bone than on the fifth, that with the feet thus forced into eversion and pronation not only is it impossible to use the full grasping powers of the feet in walking but the foot in this position must take off over the head of the first metatarsal bone instead of over all the toes. However, while every effort should be made to protect the feet from deformity and while it is true that the mechanics of the standing or walking body cannot be correct when the feet are not functioning correctly, it is necessary to realize that the feet only partly control and to a greater extent are controlled by and merely reflect the mechanics of the body as a whole in its relationship to gravity and the earth's surface.

Sweet²⁵ states that the obstacles which most commonly must be overcome before

the complete upright posture can be attained are: (a) Short calf muscles, or occasionally, too long calf muscles; (b) short hamstring muscles (biceps, semimembranosus, semitendinosus), (c) weak, undeveloped external rotators of the thigh, (d) weak, undeveloped glutei, (e) weak, undeveloped muscles of the abdominal wall, (f) strong, overdeveloped erector spinae muscles in the lumbar region and correspondingly weakened members in the dorsal region, (g) strong, short, overdeveloped anterior shoulder girdle muscles, and (h) forward thrust of the head, with shortening of the upper trapezius and splenius muscles. Much can be done to prevent these deformities in young children, and they can be corrected or greatly reduced in nearly if not all normal children later in childhood. In the hurry and bustle of modern life many children are spending too much time in the upright position. Fatigue always causes the child to slump in the posture with the lowest possible center of gravity. When this faulty posture is noticed, all too often a dancing class is added to his already too large burden of activities. Someone may notice the pronation of feet and prescribe corrective shoes which interfere with the function of his feet. He may have an acute illness and, while not yet fully recovered, he may become a victim of fatigue or some muscles may gain an advantage over their weaker opponents. His bed may not be flat and firm, forcing him to sleep in a posture that shortens some muscles and stretches others. His chair may be too deep and too high, so that when he sits in it the weight of his dangling legs pulls his shoulder girdle forward and thrusts his head forward. His teacher of physical education and his parents may still have the military posture in mind and be constantly saying "Stand up! Sit up! Throw your shoul-

ders back!" According to Sweet,²⁵ a child should not be told to stand up without being taught to do it any more than he should be ordered to do his arithmetic without preliminary instruction in fundamentals.

The great number of normal children need no attention to their body mechanics during the preschool years, except that they must be properly fed and protected during and after acute illness and that no mechanical force, such as that supplied by shoes, bed and chair and especially by overfatigue, must be allowed to interfere with normal development. However, even during these years many children need help which can be given most effectively and economically at this time in the child's life. Nasal obstruction interferes with the development of the thorax and should be remedied as soon as it is apparent by removal of the adenoid growth and relief of allergic rhinitis. Malocclusion of the jaws that evidently interferes with mastication or breathing should be corrected by the orthodontist even though some further correction may be needed after the permanent teeth are in. An attempt should be made to strengthen the muscles of the abdominal wall if they appear to be underdeveloped and especially if wide separation of the recti is present. This is best done by encouraging the child to play at the game of pulling himself into a sitting position without the assistance of the arms, from a supine position on a firm flat surface, with his legs widely separated and held firmly against the supporting surface by an adult. The wide separation of the legs is important in that it prevents the psoas muscles from pulling in a straight line and makes stronger contraction of the muscles of the abdominal wall necessary.

Certain infants who walk late and stand with the feet in extreme pronation and eversion have such long calf muscles that

the feet can be dorsiflexed far beyond the normal angle often until the dorsum of the foot is brought almost into contact with the anterior surface of the leg. These children begin walking very soon after being fitted with shoes having heels of suitable height, usually from $\frac{1}{2}$ to $\frac{3}{4}$ inch, and in time the calf muscles shorten sufficiently to correct the pronation. Certain other children early in life show a tendency to too great shortening of the calf group. Aside from their hereditary tendency, this is brought about by the extra work thrown on these muscles when a poor habitual upright posture continually keeps the center of gravity of the body too far forward. Often the feet of these children show early but unmistakable signs of becoming the rigid claw or pes cavus type of later life. Sweet²⁵ believes that no other type of deformity of the foot can produce so much human misery. Often the child with this type of foot has been complimented in classes in physical education because of his "wonderful arches" even though his contracted toes, flattened anterior transverse arches and inability to dorsiflex or extend the foot are already too apparent. If deformity is not advanced it may be corrected by the removal of such obstacles as incorrect shoes and by manual stretching of the calf muscles and plantar tendons and fascia, supplemented by stretching exercises and the natural corrective value of full function.

Sweet emphasizes that after the feet, legs, pelvis and the lower part of the spine are in balance, correction of the position of the head completes the correct alignment of the body. The correct position of the head is the most difficult to teach, and faulty position of the head with excessive cervical lordosis often remains long after other faults are remedied. He has had more success with the method described by Haynes than with

others. His method is to have the patient drop the head backward as far as possible and then revolve it up into full extension about an imaginary axis passed through the head from ear to ear. Resistance to full extension is offered principally by contraction of the anterior muscles of the shoulder girdle and shortening of the muscles which pull the head backward (upper trapezius, splenius and sternocleidomastoid). Sweet²⁵ states the best single exercise to stretch the anterior muscles of the shoulder girdle, strengthen the posterior muscles and accomplish the same result in the neck is as follows: Lie prone on a firm surface with the head extended so that the forehead rests firmly on the supporting surface; clasp the hands together over the buttocks and draw the scapulae as near together as possible toward the midline; holding the scapulae firmly fixed and being careful not to rotate the head backward, raise the head and trunk as far as possible dorsally.

PHYSICAL THERAPY IN OPHTHALMOLOGY

Gifford,²⁶ in discussing *phototherapy* in ophthalmologic practice states that such treatment is nearly always indicated in cases of phlyctenulosis when proper use of sunlight cannot be secured. With the use of a large mercury vapor or carbon arc lamp, one-third of the surface of the body is irradiated at a sitting, the dose being chosen which will produce a slight erythema. Such treatments are given to other areas twice a week and repeated until from 15 to 25 treatments have been given. Administration of calcium and vitamin D by mouth is a useful adjuvant to general phototherapy. In cases of any form of ocular inflammation affecting a person with poor general resistance, and espe-

cially in cases of uveitis considered to be tuberculosis, general phototherapy may be of considerable value and should be employed more often. The same is true of that severe and intractable condition, sclerosing keratitis. Local phototherapy has not lived up to the expectations which were held for it.

Use of Cold—In the use of cold, Gifford emphasizes the tremendous value of cold when applied after certain operations, and a simple but effective way of applying it. Anyone who will compare the results of alternate operations for squint with and without the application of cold as a routine measure can hardly fail to be impressed with the difference in the postoperative reactions. Chemosis and congestion after operations for squint with the use of cold are minimal and in many cases almost entirely absent. The effect is even more striking after simple evisceration of the globe, while without the use of cold, chemosis was always extreme and very persistent. In operations for ptosis, since the use of Friedenwald's procedure of protecting the cornea by the lower lid, it has become possible to use cold, and the results are well worth the trouble. The practical method of applying cold is that used in Dr. Loyal Davis' neurosurgical cases at Passavant Hospital and probably is familiar to most physicians. Finely chopped ice is placed in a thin rubber glove, the fingers of which are tied off so that a small flexible bag is formed. This is covered by a single layer of thin gauze and applied to the closed lids, which may be covered by a single layer of sterile gauze if skin sutures have been employed. This treatment is carried out during the alternate waking hours; it is begun immediately after operation and continued for 3 or 4 days, as a rule.

Infrared Lamps—According to Gifford²⁶ in using infrared lamps Coulter

has given experimental evidence indicating that greater heat may be produced in the tissues with infrared lamps than with heating pads, and almost the same superiority probably holds when the heat of infrared lamps is compared with that of moist hot packs. There are also practical reasons for preferring infrared lamps for routine use in the hospital or the home. Such heat is clean and may be employed after operations without danger of infection. It avoids direct contact with the lids, which is of advantage in cases of recent operation or wound. The use of lamps lessens the amount of nursing care required, as compared with moist heat, since the patient is easily taught to adjust the lamp to the limit of skin tolerance. The more expensive infrared lamps which are usually available in hospitals may be replaced by inexpensive models for use by the patient at home.

The indications for infrared therapy include all forms of inflammation of the eyes and adnexa except those in which danger of hemorrhage exists. Other exceptions are glaucoma and the early stages of conjunctivitis in which swelling and chemosis might be increased. In cases of acute iritis, postoperative iritis, acute cellulitis and deep infection of the lids, heat is especially important and may be used almost continuously.

Short Wave Diathermy—Puntenney and Osborne, in some work now being conducted at Northwestern University, a report of which will be published later, obtained results which agreed in most essentials with those of Kokott. With the same short wave diathermy instrument, the glass electrodes being placed one over the eye and the other back of the neck, the temperature in the vitreous was raised within 20 minutes to from 107° to 109° F. (41.6° to 42.8° C.). Cooling from the highest

point occurred rapidly after the current was turned off, the temperature reaching to 104° F. (40° C.) within 20 minutes and usually returning to normal within 1 hour. The body temperature was considerably higher than in Kokott's experiment, but in most animals it remained an average of 3° F. lower than that of the vitreous. When the 2 electrodes were placed on either side of the eye such high temperatures were not obtained, the maximum being 106.7° F. (41.5° C.) and the average 103° F. (39.5° C.). Cooling also occurred much more quickly with this technic. With a 10-minute exposure almost the same temperature could be reached, but cooling was much more rapid.

Of clinical reports, that of Gutsch gives his experience in treating 276 patients with ocular disease. He employed the same short wave diathermy machine as Kokott did, using glass shell electrodes held from 1 to 3 cm. from the globe, with exposures beginning at from 6 to 8 minutes and being increased to 15 minutes in certain cases. Treatments were given 2 or 3 times a week. He saw no evidence of damage in any case. He saw no definite beneficial effect in cases of corneal disease, glaucoma or scleritis, and the effects in cases of acute iritis were doubtful. He was impressed by the benefits obtained in cases of chronic iridocyclitis, especially the tuberculous form, and in cases of vascular disease of the fundus. In 3 cases of conglomerate tubercle of the iris and 2 of conglomerate tubercle of the choroid the lesions disappeared rapidly under treatment. In cases of acute orbital cellulitis and acute dacryocystitis the inflammation subsided rapidly.

In discussing fever induced by long or short wave diathermy, Gifford²⁶ states that there can be no doubt that when fever therapy is indicated, the increase

in temperature can be efficiently and constantly obtained by diathermy. The blankets with which long wave diathermy was employed have rather generally been replaced by cabinets in which a field of short wave current is generated while the patient is kept dry by the passage of air. The desired temperature can be produced more rapidly in such cabinets than in those employing air conditioning alone. Even when every precaution is taken to replace lost fluid and salt during the treatments, the methods are not without danger. Hence it should be reserved for serious conditions which do not respond to other forms of therapy and must not be employed for elderly or infirm patients, especially if increased blood pressure or myocardial lesions are present. It is the routine at the Passavant Hospital to require an electrocardiographic examination in addition to a thorough physical examination before fever therapy in the cabinet is given. The treatment must be supervised throughout by an assistant who is thoroughly familiar with the method and with complicating conditions which may arise during treatment.

Uveal Tuberculosis

According to Meyer²⁷ uveal tuberculosis occurs only in an individual who has tuberculosis elsewhere, for it is always secondary. There are 2 main types of responses in the uveal tract to tuberculosis: (a) A tubercle, and (b) exudative lesions.

In the treatment of uveal tuberculosis Meyer²⁷ states that general curative measures such as *rest, diet, heliotherapy*, etc., are as much indicated in eye tuberculosis as in pulmonary or other tuberculosis. Their importance has been emphasized by many observers, for many cases will be retarded or completely fail

in their recovery until these measures are applied.

Corneal Ulcers in Childhood

Doggart²⁸ states that in this country measles and phlyctenular disease are the most important causes of corneal ulcers in childhood. He believes that improper food not only predisposes a child to ulceration of the cornea, but also aggravates any ulcer that already is present. Personal uncleanness is another aggravating factor, to be emphasized with reference to phlyctenules. Dust also can help to do damage, so that intractable, relapsing corneal ulcers commonly occur. According to Doggart, in corneal ulcers associated with keratomalacia, and in many of those that come under the heading of "neuropathic," there is a striking absence of most of the typical symptoms and signs. With these exceptions, however, most corneal ulcers are attended with a certain amount of pain. Severe pricking pain is particularly associated with superficial erosions, which are often multiple. Deep ulcers attended with large destruction of corneal substances are often far less painful; and when they do cause much pain, this may be the result of raised tension from increased viscosity of the aqueous fluid. Photophobia, *i. e.*, reluctance to open the eyes except in the dark, often is a prominent symptom.

According to this author phlyctenular disease is much less common in our cities than it was 30 years ago. A raised standard of living for the wage earners, improved social services, and increasing supervision of school children's eyes are chiefly responsible for this change. In the nineteenth century the disease was regarded as tuberculous by many ophthalmologists, but doubt was cast on this etiology by repeated failure to identify the tubercle bacillus in the actual lesions.

Recent researches, however, by Sorsby and others suggest that the tubercle bacillus situated elsewhere in the body is a potent factor in causation.

Doggart states that in treatment gentleness of manipulation, avoidance of drastic measures and attention to the general health are the main principles of treatment. The eyes should be *shielded from excessive light*, either by keeping the patient in a darkened room, or by dark glasses, or by shading the eyes. *Normal saline solution* or some other mild lotion should be used several times a day according to the amount of discharge present. Among infants or small children with much lid spasm, it is better to avoid frequent irrigation when they have to be treated as outpatients. Unskilled irrigation may do more harm than good, especially if performed with that lack of attention to cleanliness which prevails in so many households. One per cent *atropine ointment* is safe and advisable in most cases. The custom of combining this ointment with yellow oxide of mercury is less favored nowadays, because the latter substance has a definitely irritant effect on many subjects. Large ulcers extending dangerously may have to be carbolyzed. Diet must be regulated to be as palatable and nourishing as possible. *Malt* and *cod-liver oil* are useful adjuncts. A course of general *ultraviolet light* is often helpful. *Removal of enlarged tonsils* will work wonders in a certain proportion of cases which have obstinately resisted other forms of treatment.

SPAS AND HEALTH RESORTS

Fantus²⁹ believes that it still remains to be shown that the use of bottled mineral waters or of salts gives better results than the employment of an appropriate mixture of similar salts that any pharma-

cist can prepare. Experience has definitely proved, however, that the therapeutic value of a mineral water taken at the patient's home is usually much inferior to the use of a similar water at a mineral springs resort; for some of the important ingredients of the "cure" are missing. These are the remedial value of a vacation, the change of scene and of occupation, the change in the mode of living, the subtle influence of climate and the factor of faith.

A spa is a health resort that has one or more therapeutically valuable mineral springs. Fantus²⁹ states that quite as important as the choice of the proper climate is the choice of that variety of mineral water which will exert the most favorable possible influence on the patient's functions and metabolism in those cases of disease amenable to such therapy. Since similar mineral springs may be found in greatly diverse climates, the correct selection of a spa is a test of the physician's knowledge of both climatic therapy and pharmacotherapy.

A principle not sufficiently appreciated in connection with the drinking of mineral water is that the most important constituent of mineral waters is the water, mineral waters being, with few exceptions, very dilute solutions of salts. The saline ingredients of mineral waters in many instances serve merely to point the path the water is to take in its elimination from the system. If the water is associated with poorly absorbed saline ions, it will be eliminated chiefly by way of the bowel in the form of liquid stools. If it has ions that escape chiefly through the kidneys, diuretic action results. If it contains ions that are eliminated by the mucous membranes, a thinning of mucus with improvement in conditions of the various mucosae may be obtained. Hence spa therapy is decidedly advantageous in the treatment of constipation, cholelithia-

sis, nephrolithiasis and cystitis as well as bronchitis with scanty expectoration. The desired effect is secured provided only that a sufficient amount of water is ingested at one time. It must be realized, however, that the drinking of large quantities of water is not always advisable. It is contraindicated in such conditions as motor insufficiency of the stomach, cardiac insufficiency, nephritis, edema from any cause, aneurism, arteriosclerosis and tendency to internal hemorrhage.

Fantus states: "With over 2000 places in the United States boasting of springs of more or less medicinal value, with the possibility of commanding watering places in almost any climate and at any season, the members of the medical profession are so poorly informed about them that, when need for spa treatment arises, they are more likely to know a suitable European spring than one in this country. This is because textbooks and teachers have more to say about the latter than the former. Distrust and skepticism likewise prevail regarding our mineral spring resorts. With a few notable exceptions this is well merited, for the mendacity of many of the advertisements for mineral springs rivals that of the claims for 'patent medicines' in their palmiest days. Unethical practice and quackery abound in and around health resorts. Even the social features and amusements, in many of them, may be objectionable from a therapeutic as well as moral standpoint."

Capener³⁰ in considering the management of rheumatoid arthritis believes spa treatment is helpful in the management of this condition. He states that it should be premised that there is nothing specific in the waters of the spas in this or any other country as a cure for rheumatoid arthritis. The advantages of spa treatment are the removal from home surroundings to a new and healthy environ-

ment and the psychological element of hope; the availability at any well-equipped spa of a wide range of physical treatments, hydrological and balneological; access to medical advice from practitioners of special knowledge from long experience with the disease; facilities for thorough investigation, bacteriological and biochemical, necessary for diagnosis and control of treatment; and the use of natural mineral waters for the correction of metabolic derangements and the improvement of general health, so necessary a part of a concerted attack on the disease. The disadvantages are the expense entailed in a spa cure, which must necessarily be prolonged if good results are to be achieved. In so chronic a disease swift improvement cannot be affected in a short space of time. Nevertheless even in a limited period a start may be made and a patient be put on the high road to recovery, which may be followed up at home.

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SURGERY

Edited by W. WAYNE BABCOCK, A.M., M.D.

ABDOMINAL SURGERY

Edited by JAMES NORMAN COOMBS, M.D.

Introduction — In any consideration of abdominal surgery, *pain* is one of the most important symptoms leading to a correct evaluation of the disease to be treated. A knowledge of the source of pain and its distribution is necessary in diagnosis. The mechanism of visceral pain originating in the gastrointestinal tract is outlined by J. Morley¹. The one stimulus adequate to produce direct visceral pain in the gastrointestinal tract appears to be tension on the afferent nerves in its muscular coats, and this tension usually is caused by spasmodic and exaggerated peristaltic contraction. The sensitive mesentery often is involved in such lesions as strangulation and volvulus, and this causes a combination of visceral and somatic pain that is not easy to unravel. The nerves of the sensitive parietal peritoneum must receive the stimulus that gives rise to the pain and tenderness in the superficial parts of the abdominal wall and to the associated reflex muscular rigidity.

The process is described as peritoneocutaneous radiation and a peritoneomuscular reflex. An appreciation of this peritoneocutaneous radiation is essential for any true understanding of abdominal pain, and the mechanism is best illustrated by stimulation of the phrenic nerve terminals below the diaphragm. When the undersurface of the central portion of the diaphragm receives a painful stimulus, immediate pain is felt in the region of the descending branches

of the third and fourth cervical nerves supplying the skin of the supra-acromial region. Infiltration with procaine hydrochloride of the area of skin supplied by the third, fourth and fifth cervical nerves either abolishes or greatly modifies the referred pain caused by stimulation of the diaphragm.

A study of phrenic pain leads to the conclusion that a precisely similar peritoneocutaneous radiation occurs in the superficial nerves of the anterior abdominal wall when the underlying parietal peritoneum receives a painful stimulus from an inflamed viscus or inflammatory exudate. The localizing pain in acute appendicitis or acute cholecystitis is greatly modified or completely abolished by inducing local anesthesia by subcutaneous infiltration of the area in which the pain is felt. Whatever the ultimate truth may be as to the mechanism of referred pain in angina, the author contends that it differs fundamentally from the mechanism of pain in the gastrointestinal tract, in which there certainly is a dual mechanism. On the one hand, one sees true visceral pain as part of a defense against the threat of obstruction. It is primitive in the scale of evolution, is in no sense referred to the superficial somatic nerves and is imperfectly and vaguely localized. On the other hand, one finds referred pain, the stimulus for which arises not from the visceral afferent nerves at all but from the somatic nerves of the parietal peri-

toneum. It has been evolved as a protection against bacterial infection of the peritoneum, either by penetrating wounds from without or by perforation of the intestine within. It is later in the scale of evolution and produces a radiation of pain to the superficial somatic nerves and a reflex protective rigidity of the overlying muscles, both of which are localized accurately.

Unless there are sensible reasons for surgical treatment, debilitated patients suffering from chronic wasting diseases as tuberculosis, pellagra, cardiovascular disease, nephritis, extreme old age, anemia and inanition should be treated by medical measures until they are fairly good surgical risks or not operated on at all.

K. H. Aynesworth² states that distention merits the closest scrutiny whether the patient has been sick for a few hours or for days. There is more surgical significance in this one sign than in all other except actual impending death. Distention of any extent, but especially when marked, interferes with all operative procedures and makes the operation difficult and tedious if not prolonged, thus increasing the danger of surgical intervention. Occasionally, cutaneous infections are a potential danger if an incision is made through such an area. When the pulse rate is high, associated with a normal heart or with a diseased heart, the surgeon should carefully weigh the consequences of an abdominal operation.

More important than either the pulse rate or the abdominal distention, when considered alone, is the blood pressure if it is very low. When the blood pressure remains normal even though other symptoms of grave danger are present, the surgeon may take risks which would be inadvisable if the pressure was below normal. A marked drop in the blood pressure, in association with abdominal

distention and a rapid pulse rate, cannot be overestimated.

The presence of these 3 symptoms in combination, irrespective of the previous condition of the patient, is a positive contraindication for operation. Cardiac irregularity, valvular murmurs, hypertrophy or high blood pressure alone are not contraindications to surgical measures; but, when associated with the foregoing conditions, any cardiac disturbance augments the danger. If distention, rapid pulse and low blood pressure are present in a patient presenting an acute abdominal crisis complicated by pneumonia or pleurisy, operation is absolutely contraindicated. If the so-called dangerous and absolute symptoms are not present, the surgeon should individualize each patient and operate according to his judgment. Severe acute anemia from any cause, recent hemorrhage, chronic hemorrhage, disease of the blood-forming organs, recent illness and the like are all to be weighed carefully before deciding to operate in a delayed or neglected acute abdominal case. Operation should be delayed until remedial measures have been given and the patient's improvement is assured.

Blood dyscrasias, as acute leukemia and similar blood diseases, are contraindications for operation in the late stages of any acute abdominal disease. Hypoglycemia and hyperglycemia in diabetic patients should be corrected before operating for a late abdominal infection. Alkalosis and acidosis, if marked, should cause the surgeon to hesitate until appropriate remedies have been begun and the patient's condition has improved. Acute insanity is a contraindication to operation unless the operation is undertaken early in the disease.

Delirium from any cause, especially alcoholic or from other drugs, is a serious complication if not a positive contra-

indication to any serious surgical procedure, especially abdominal operations. Operation should be delayed until the patient has recovered from this state. If the delirium is due to some cerebral disease, any operation is contraindicated except that designed to treat the condition causing the trouble; no abdominal operation is justified.

When the patient is at the point of death from any cause, operation should not be performed unless it is urged by those responsible. Shock is a contraindication—with the debatable exception of shock from hemorrhage—for any abdominal operation. Pregnant patients do not have normal resistance to infection. If possible, they should be carried over until every precautionary measure has been used before operating to prevent strain on the reserve store of vital resistance.

Ultraviolet Light During Laparotomy—The favorable experience of J Wicke³ with the use of filtered ultraviolet light during laparotomy in the first 85 cases of 1933 led to the further use of this procedure in 398 cases. The first group of cases include 71 cases of general suppurative peritonitis, 45 of which were the result of perforative appendicitis. The others were perforations of the gall bladder, the stomach, and of the common bile duct from cancer of the rectum. The second group includes 206 cases of acute inflammation of organs lying within the abdominal cavity with more or less marked, but always circumscribed, inflammatory involvement of their serosa and of the neighboring organs, such as perityphlitic abscess, phlegmonous or subacute appendicitis, incarcerated hernias, and acute pancreatitis. The third group consisted of 110 cases of chronic inflammation of the peritoneum or of the abdominal viscera, such as chronic appendicitis and cholecystitis. The fourth

group were 11 cases of experimental irradiation of cancers of the abdominal organs, including 1 joint, and the wound areas of various operations.

The first group showed the most marked effects of the laparophos lamp. Only 20 per cent of the patients died, and of those with inflammation of the appendix and peritoneum only 16 per cent. In these cases the Clinic did not follow strictly the principles of Havlicek. Except in 4 cases they always drained the abdominal cavity with drain and gauze, and operated not only under local, but often under general anesthesia. They irradiated an exposed coil of small intestines placed on a moist compress, peritoneum, or the operative area itself, with the use of the Helluvial filters for from 5 to 25 minutes. With this technic, hyperemia and occasionally even peristalsis appeared.

The favorable signs after the operation were: (1) Diminution of the pains, (2) early appearance of peristalsis; (3) disappearance of the peritonitic symptoms, (4) increase of blood pressure, and (5) general well-being. The absence of adhesions and the diminution of peritonitic adhesions and exudates could be demonstrated at relaparotomies.

Postoperative Gangrene of Abdominal Wall—Since most septic operative wounds of the abdominal wall are amenable to ordinary treatment, and progressive postoperative gangrene of the abdominal wall is rather rare in the experience of the average surgeon and its early recognition and treatment are important, A E Hiebert⁴ lists the main features of this now apparently established clinical entity progressive necrosis about an operative abdominal wound, which does not respond to the ordinary methods of treatment; severe local pain and tenderness; slight rise in temperature or leukocytic reaction; general men-

tal depression of the patient. The etiological organisms are streptococci and staphylococci. Treatment short of complete cautery excision of the entire lesion is likely to be inadequate.

Postoperative Illness — R. Leriche⁵ maintains that the chief cause of postoperative illness is not infection nor chemical changes, but trauma to the nervous system and especially to the vasomotor mechanism. So-called postoperative complications, such as shock, pulmonary collapse, and phlebitis, are but "exaggerations" of the normal phenomena produced by operation. Infection and hemorrhage are true complications and not a part of postoperative illness.

Postoperative illness is produced essentially by vasomotor reflexes from the region of the wound. Shock is the most severe form of this postoperative vasomotor depression.

The usual discomfort experienced by the patient after operation, pains, thirst and the retention of urine, is the second form of this illness. This usually subsides spontaneously, but it may be exaggerated and prolonged if the traumatism has been considerable and the signs of overstimulation of the sympathetic system are exaggerated.

Pulmonary collapse is also an exaggeration of the retraction of the periphery of the lungs which may usually be demonstrated radiologically after operation or, as the author has repeatedly shown, even while the patient is on the operating table.

The modifications of the blood, especially the usual increase in blood platelets that follow operation, may cause thrombosis and phlebitis.

Another form of postoperative illness is the toxemia that clinically appears later; this the author believes is caused by humoral changes that in reality occur early. These changes are due in part to

local tissue destruction, but probably to a greater extent to lysis of proteins at a distance caused by sympathetic nervous system reflexes.

These findings suggest measures for the prevention of postoperative illness. In the first place, it is important to avoid injury to the tissue at the site of operation by careful handling. In the second place, it is necessary to employ local anesthesia as far as possible; the author has used local anesthesia in 6757 in 19,650 operations, or about one-third. This experience has shown that local anesthesia is definitely of advantage in reducing postoperative illness by blocking the centripetal conduction in the zone of operation. The third factor is to effect careful hemostasis because loss of blood facilitates vasoconstrictor reflexes and shock. The fourth factor is to employ transfusion of blood after any severe operation, such as gastrectomy or subtotal thyroidectomy; this procedure aids in establishing the equilibrium even if there has been no excessive blood loss. Also, the local application of the infrared rays is of value in reducing postoperative malaise; it acts apparently by increasing local hyperemia and thus possibly diminishing the absorption of proteins.

The author is of the opinion that postoperative illness as ordinarily described is the type that follows abdominal operation. The symptom following operations in other tissues are of a different type according to the site of the operation.

Abdominal Injuries

The literature contains many isolated case reports of abdominal injury but comprehensive reviews are not as common. In private practice, the number of cases of abdominal injury is usually limited. In industrial practice, this number is steadily increasing. In wartime, the pressure of work and unfavorable cir-

cumstances under which it must be conducted, militates against thoughtful observation or improvement. It is chiefly on the service of large general hospitals in peacetime that the material is adequate and the facilities for painstaking work are sufficient to encourage progress.

Before anesthesia and asepsis, surgeons in general were reluctant to accept

It is agreed in the literature that the policy of prompt laparotomy in penetrating wounds of the abdomen is definitely an American contribution. This is ascribed to the abundance of peace-time material in America, "where it is the general custom to carry firearms, and to use them on little provocation." The tendency to violence and the disregard for

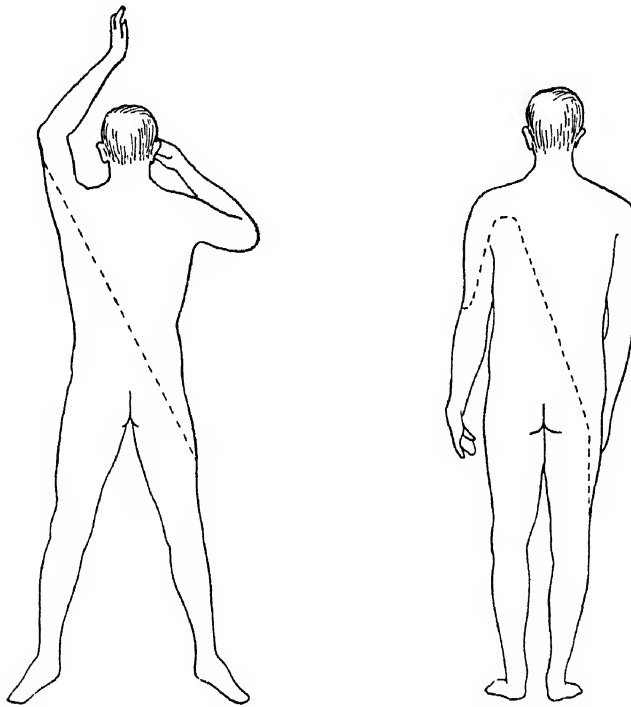


Fig. 1—Left. Course of bullet at time of wound infliction when patient was in typical prone rifle position. Right. Apparently bizarre course of bullet when patient is on examining or operating table. (Surg., Gynec. and Obst. 66:248 (Mar.) 1938.)

this advice. During the Civil War, an abdominal wound was partially enlarged and some attempt at intraperitoneal hemostasis and suture was made only occasionally. The mortality was over 90 per cent. By 1900 it was decreased to 75 per cent. In the early years of the World War, the factors of delay and poor operating conditions proved so disastrous that the operative treatment of abdominal wounds was discouraged. In the later years these factors were corrected and mortality fell to from 50 to 60 per cent.

human life was increased further by the World War. The number of cases of bullet wounds in the Cook County Hospital was abruptly doubled after the War. Since 1920 the mortality statistics have remained stationary. Occasional better controlled series which have been reported encourage the conviction, however, that careful preparatory and operative work, analysis of the pertinent factors, and a wider diffusion of the knowledge so gained will substantially improve the general results.

Treatment—K. Meyer and P. F. Shapiro⁶, in summarizing treatment of abdominal injuries, state that the policy of *prompt exploration* in *penetrating* wounds of the abdomen is established. However, no patient should be subjected to laparotomy until proper preparation has brought his blood pressure above 80, unless the operation is one of "last resort."

Secondary shock on a surgical service is equivalent to hemorrhage, and until the

wounds at a distance are best managed by conservative management without operation.

Bullets do not take erratic courses within the abdomen but practically always follow a straight line. Following and filling in this straight line is one of the best assurances that no perforations have been overlooked

Free muscle grafts assist in *hemostasis of the liver or kidney*. In massive injuries of the liver, *tamponade* is safer;

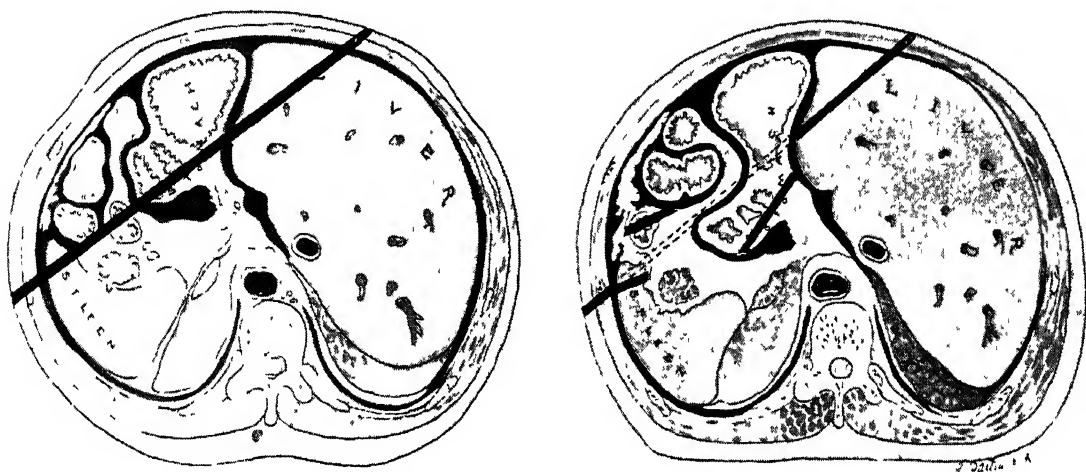


Fig 2—Left Bullets take a straight line Cross section of body midway between xiphoid process and umbilicus Solid and hollow viscera and abdominal wall in positions they occupy as patient is standing or sitting as at time of assault Path of bullet is straight Right Patient lying on operating or examining table Solid and hollow viscera and abdominal wall have shifted from their previous relative positions so that the bullet is now apparently erratic These broken lines can be aligned during exploration into a straight trajectory (Surg, Gynec and Obst 66 249 (Mar) 1938)

bleeding vessels are ligated should not be treated by intravenoclysis but by *blood transfusion*.

Patients operated upon in shock are not only less likely to survive the operative trauma, but are almost certain to succumb to peritonitis eventually. Correction of shock increases the resistance to peritonitis

Stab wounds are not as serious as bullet wounds even when eviscerations are produced

Shotgun wounds at close range are usually immediately fatal Shotgun

in those of the kidney, *nephrectomy* may be required For even moderate wounds of the spleen, *splenectomy* is safer because of the danger of late hemorrhage

Pedicled-muscle onlay grafts assist in the repair of large vessels.

Bowel perforations are closed with the simplest technic which will give hemostasis and peritonealization Resections are avoided if possible, but they may be required by multiple adjacent perforations or by impairment of the bowel viability.

For colon perforations, *proximal ventilation* or *deflection colostomy* is recommended.

Perforations of the urinary bladder are closed by catgut suture to avoid secondary stones. The bladder must be kept decompressed.

The general peritoneal cavity is not lavaged and is not drained. Retroperitoneal tissue if exposed are *drained*. The abdominal incision is drained also.

Anti-gas-bacillus serum and *tetanus antitoxin* are given routinely.

tients have pseudoperitoneal syndromes or injuries which either do not require laparotomy or cannot be benefited by it.

Shock treatment is started, however, and laparotomy is performed if signs of peritoneal irritation persist, internal hemorrhage does not stop, or special tests reveal probable injury of a hollow viscus. The absence of a gas bubble does not exclude the possibility of rupture of the small intestine, and suspected cases are operated upon in preference to risking fatal delay.

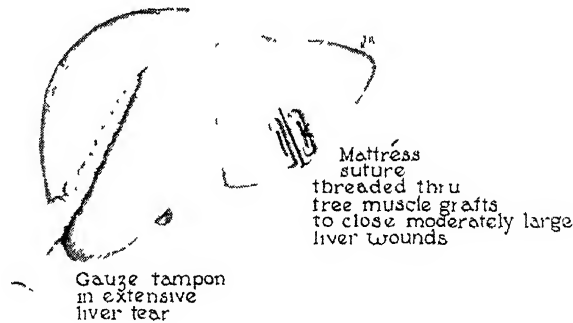


Fig. 3—Methods of controlling extensive and moderately large liver wounds. The tampon is a method of extremis. The free muscle grafts cushion the suture and furnish thrombokinase for hemostasis; a third piece of muscle may be inserted in the wound cleft. Small wounds may be sutured simply, or disregarded. (Surg. Gynec. and Obst. 66: 250 (Mar.) 1938.)

Postoperative transfusions, intravenous glucose and saline solutions, constant suction by means of the nasal tube, adequate *morphine*, and *good nursing care* are essential. Apparently hopeless situations may be saved by conscientious, tenacious aftercare.

The *prognosis* depends chiefly on the amount of hemorrhage, the condition of the patient at operation, the severity of the visceral damage, the time elapsing until operation, the surgical experience, and the aftercare.

In closed wounds of the abdomen the chief problem is diagnosis, but speed and proper preparation are also important.

Conservatism is in general the best policy because 70 per cent of the pa-

Careful supervision is continued, especially in those patients not operated upon, because of the frequency of late sequelae.

Primary Retroperitoneal Tumors

These tumors, although unusual, occur with sufficient frequency to make it advisable for the surgeon to familiarize himself with the subject.

R. T. Frank⁷ states that they develop retroperitoneally behind the intra-abdominal viscera. Mesenteric and omental growths are not included in this presentation.

The majority of the growths are of mesodermal origin (72 per cent). The remainder are of ectodermal (neuro-

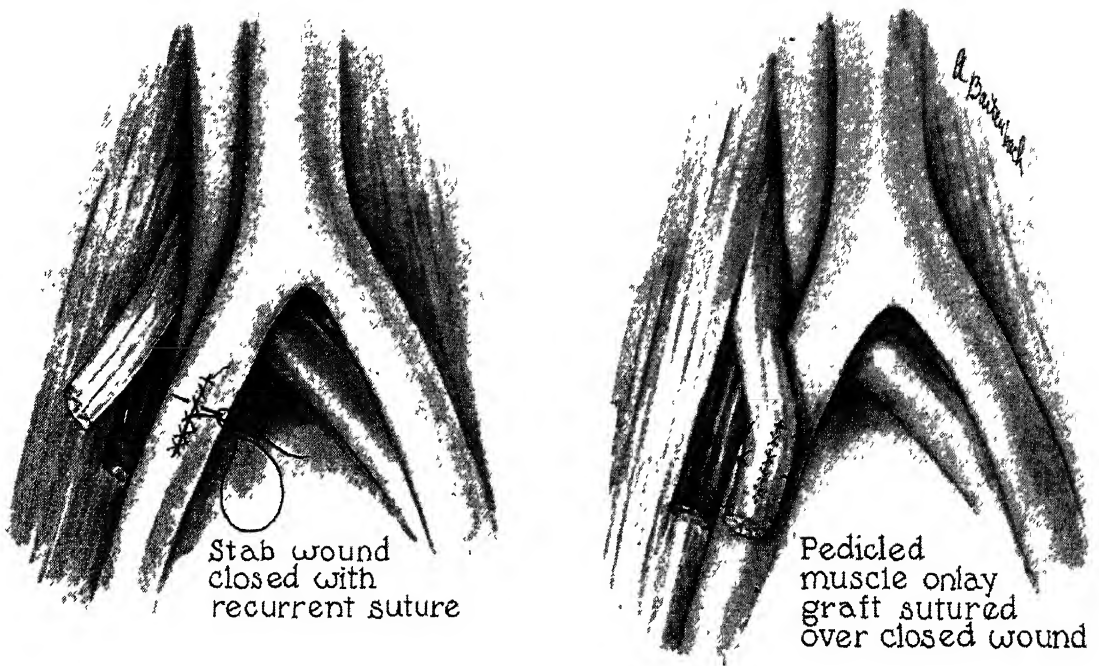


Fig 4—Left Continuous recurrent suture of fine silk in stab wound of iliac artery. The vessel must be controlled during repair by proximal and distal provisional hemostasis by the sling-tape, bulldog clamp, or Spivack clamp methods. Right Graft from psoas muscle raised and sutured to the vessel to buttress the arterial repair (Surg, Gynec and Obst. 66:251 (Mar) 1938)

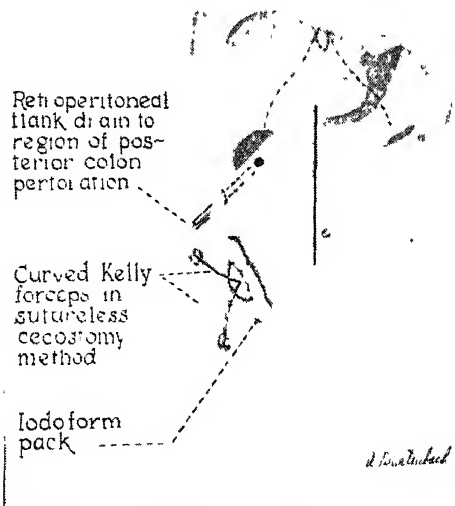


Fig 5—Principal drainage methods used. Penrose drain to retroperitoneal tissues. Cecostomy to secure low intestinal decompression and intraluminal drainage. Incision is drained to, but not into the peritoneum. (Surg, Gynec and Obst. 66:252 (Mar) 1938)

genic, 18.7 per cent) or from totipotent germ cell derivation (teratomas, 9.3 per cent).

Tumors may attain huge size; those weighing up to 69 pounds have been reported. They may be solid, cystic, or

malignancy, myxomas; definitely malignant, sarcomas, neuromas, and teratomas.

In the present series recurrences were noted in 14 (13 per cent); metastases, in 4 (3.7 per cent). In the older series 33 per cent metastases were found

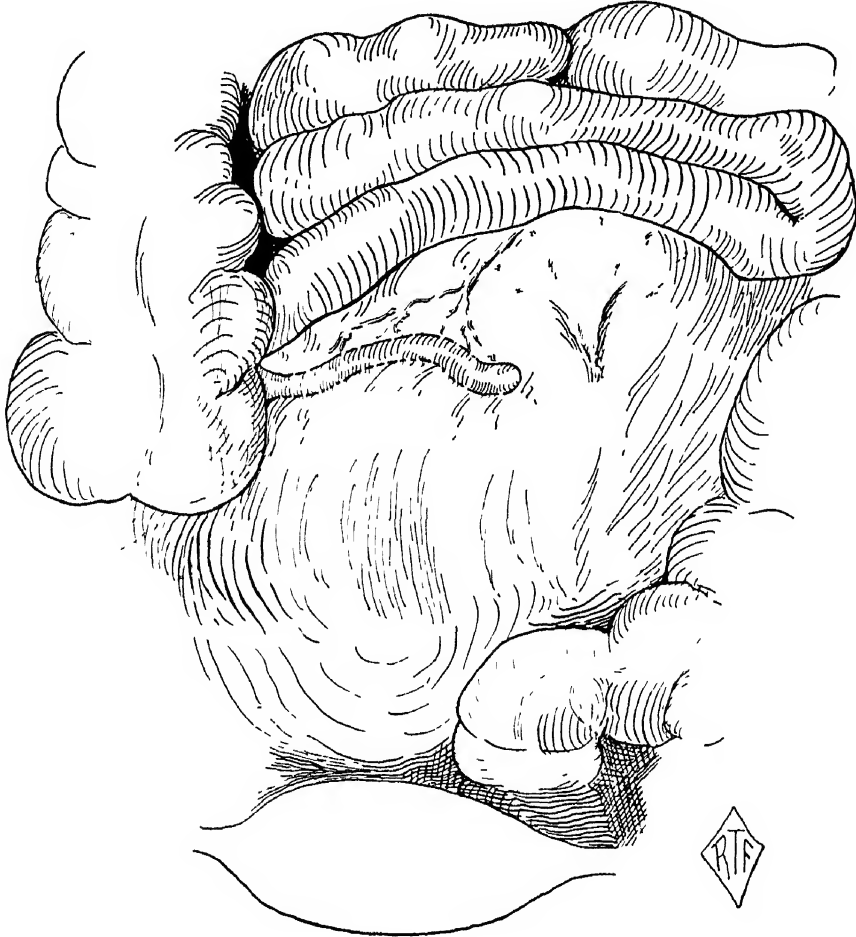


Fig 6—Case 2 Conditions on opening abdomen. Horizontal appendix, leaves of mesentery of small intestine separated by the growth, lower ileum fixed horizontally, mesosigmoid invaded. (Surgery 4:566 (Oct) 1938)

a combination of both. With the exception of the round cell sarcomas, the majority are well encapsulated. Multiple, often unconnected masses, are frequent and particularly in lipomas and myxomas account for "recurrences" if overlooked.

The histology shows benign lipomas, fibromas, and cysts; of doubtful clinical

The clinical symptoms are not characteristic. Loss of weight and strength, an abdominal mass (central or lateral), and vague digestive disturbances are the rule.

Without operative intervention a fatal outcome from the increase in size and the pressure exerted may be anticipated even from benign growths.

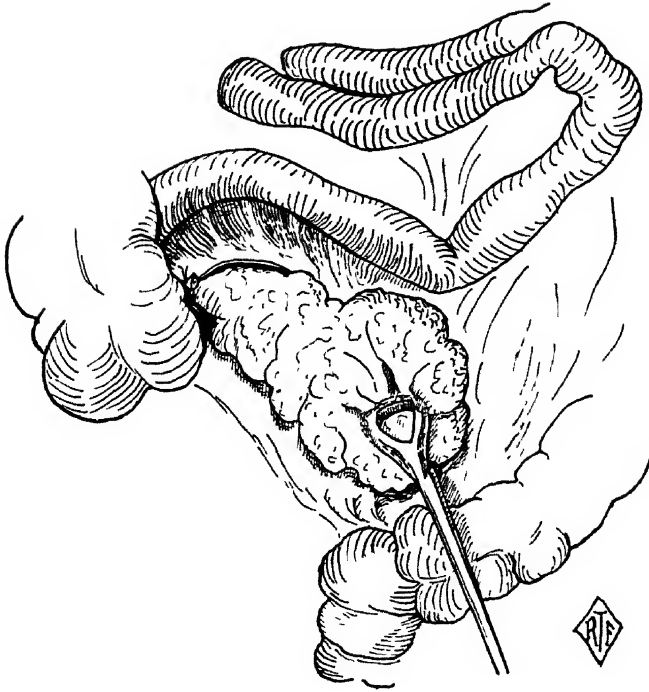


Fig 7—Case 2 First stage in development of tumor. Appendix removed, tumor freed from between leaves of mesosigmoid. (Surgery 4: 567 (Oct) 1938)

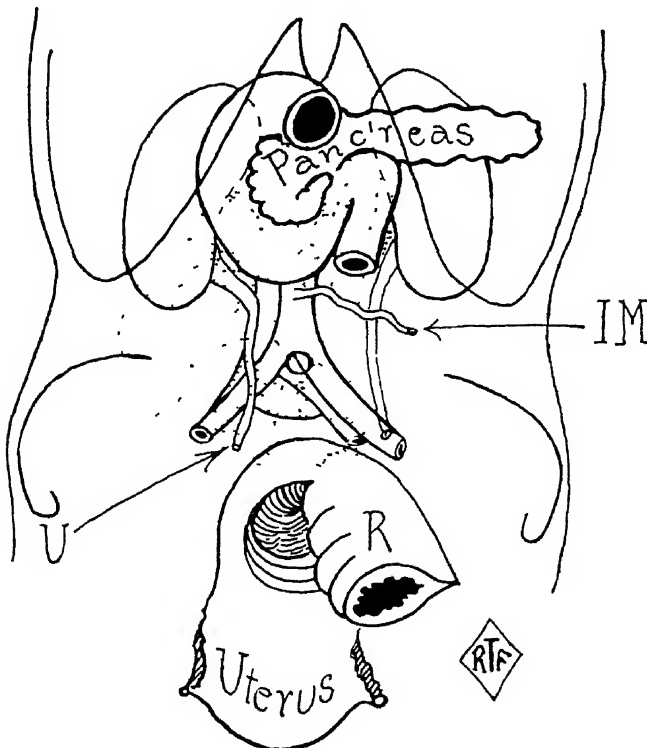


Fig 8—Case 2 Schema of retroperitoneal area, showing extent of growth (Surgery 4: 567 (Oct) 1938)

Gastrointestinal x-ray and pyelography may aid in the diagnosis by excluding intrinsic intestinal and renal growths.

Depending on the sex, site, and associated symptoms, the preoperative diagnosis most often is that of fibroids, ovarian cysts, hypernephroma, tuberculous peritonitis.

Treatment—Imperative indications for operation may arise if ileus, hydro-

gressively in myxoma (18.18 per cent), neurogenic tumors (22 per cent), sarcoma (28.13 per cent), to teratoma (36.7 per cent).

Radiotherapy (radium pack, high voltage x-ray) is indicated in all inoperable cases and in all incompletely operated cases. It is recommended postoperatively except if fibroma or lipoma is encountered.

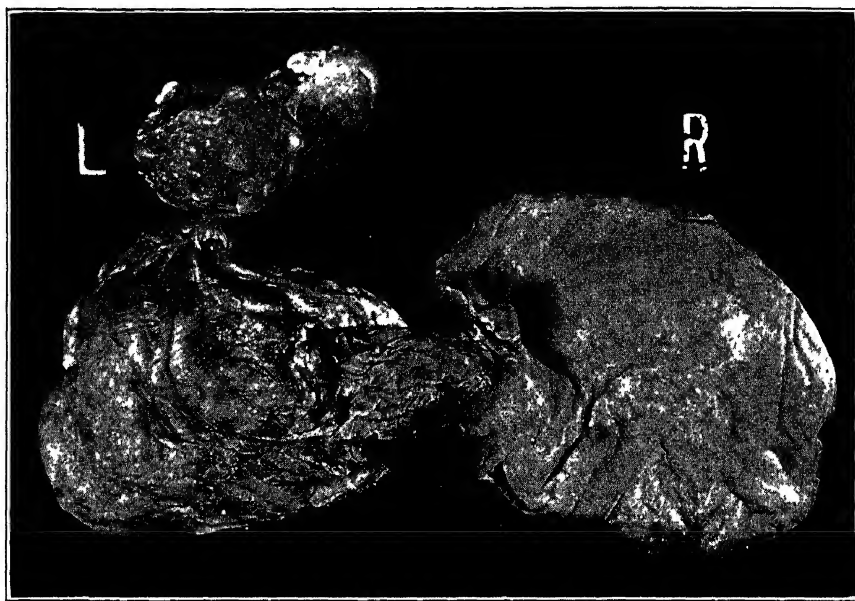


Fig 9—Case 2 Specimen Two large flat masses joined by an isthmus situated over the division of the aorta. Smaller pedunculated growth near tail of pancreas and left crus of diaphragm. Weight, 4 pounds (Surgery 4 568 (Oct) 1938)

nephrosis or pyonephrosis, or intraperitoneal hemorrhage supervenes.

Operation offers the greatest prospect of cure. In the series of 107 cases, deducting the 8 autopsy reports, only 10 were found inoperable (10.1 per cent). Of these 10, 3 were alive 1 to 2½ years later after radium and x-ray treatment.

Transperitoneal approach was utilized in 66, lumbar or combined in 13, not stated in 19 cases.

The operative risk incurred depends mainly upon the histologic type of tumor. Mortality was zero in fibroma, lipoma, and cyst; it increased pro-

gressively in myxoma (18.18 per cent), neurogenic tumors (22 per cent), sarcoma (28.13 per cent), to teratoma (36.7 per cent). Three new cases are reported—embryonal mesodermal tumor (exploratory), radium pack and deep x-ray, well 8½ years; myxoliposarcoma, operated, postoperative x-ray, well 1¼ years; retroperitoneal cyst, marsupialized, well 6 years.

Carcinoma of the Abdomen

Malignant tumors arising within the peritoneal cavity usually are primary in the stomach or intestines. The most common situations in the stomach are sigmoid and pelvic colon of the male and the reproductive organs of the female.

Carcinoma of the stomach accounts for 20 to 40 per cent of all cancers. In the colon 60 per cent occur in the sigmoid and rectum and 40 per cent involve the colon above the sigmoid. Carcinoma of the small intestine comprises 3 per cent of intestinal cancers. Occasionally carcinoma will occur in the biliary tract and pancreas. Other carcinomas are less common.

In any consideration of carcinoma, the early *signs* and *symptoms* and their common interpretation have a direct bearing on the outcome of the disease. Unexplained dyspepsia unaided by the usual treatment in a patient of the cancer age, along with loss of weight, strength and anemia, are very suggestive signs of malignancy within the abdomen. Special symptoms relating to various organs will aid in localizing the tumor. Ominous symptoms in stomach lesions will be progressive indigestion, distaste for food with achlorhydria; in the small intestine, signs of obstruction; in the large intestine, alteration in bowel habit with melena. The painless jaundice of pancreatic carcinoma and the bleeding of uterine cancer are significant. Other malignant tumors in characteristic location within the abdomen are expected to present physical signs and symptoms for early diagnosis, as described in succeeding chapters

To confirm diagnosis, the use of x-ray examination is invaluable in lesions of the gastrointestinal tract. This is particularly true of growths above the recto-sigmoid. It is to be remembered that digital examination of the rectum, aided by the proctoscope, may diagnose 60 per cent of lesions of the colon. Eighty per cent of obstructive lesions of the bowel in the elderly are due to carcinoma. In doubtful cases, repeated examinations should be made, with a thorough under-

standing on the part of the patient as to his condition.

Late diagnosis of abdominal carcinoma when obvious objective signs of mass and metastatic phenomena appear, render a poor prognosis. Results of resection of the stomach and large intestine for early cancer in the hands of the experienced are too well known to be disputed. Most of the difficulty in the management consists in the operability of the patient at the time of presentation for treatment. Lahey has shown that only 22 per cent of cases of carcinoma of the stomach are operable, whereas operability in cancer of the rectum has increased from 54 to 70 per cent.

Naturally the curability of abdominal carcinoma in the large majority of cases will depend on early interpretation of symptoms by patient and physician alike. Particular emphasis in education to show the results of early surgery should be presented more often to the individual, so that the advantages are known.

Abdominal Adhesions

It undoubtedly is true that not only are the etiologic factors of adhesion formation insufficiently appreciated; but that also the importance of abdominal adhesions has been somewhat overestimated. This does not, of course, mean that we should not continue to attempt to find some harmless method of controlling or preventing their formation. Occurrences of intestinal obstruction from them in themselves make achievement of the latter desirable. J. K. Donaldson⁸ states that such a tremendous amount of misdirected investigative work has been and continues to be done, however, that it shows that we have been unable to separate sufficiently the better work from the less desirable; or to appreciate fully fundamentals which have already been proved. Hertzler should be

given full credit for his long and laborious efforts on the peritoneum. The author's own results, as outlined in this presentation, have increased his respect for Hertzler's opinions on the subject

To operate most effectively against the production of abdominal adhesions

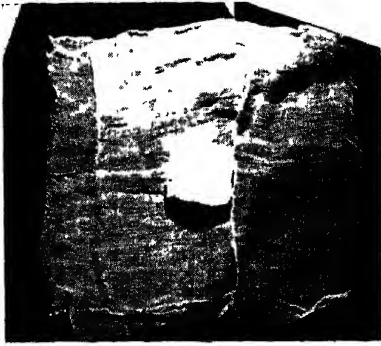


Fig 10—The cotton base sponge is shown resting in the center of a piece of gauze 15 by 17 inches. In making an ordinary gauze sponge, this large piece of gauze would simply be folded, fringed edges under. This sized piece of gauze will wrap almost 4 of the cotton base sponges, and it is estimated the latter are 50 per cent to 75 per cent more economical, if properly used, than the gauze ones. (American Journal of Surgery Vol. 39 (Jan.) 1938)

in the light of our present knowledge, one should do the following things

1. Familiarize himself with the behavior of, and different peritoneal reactions produced by, different microorganisms, realizing that the irritating toxins produced by many bacteria call forth either fibrillar (permanent) or granular (temporary) fibrin, depending upon the number and character of the microorganisms present

2. Avoid as much as possible the introduction of drains or other foreign materials into the cavity, as well as unnecessary trauma in general

3. Leave no raw endothelial edges or surfaces if avoidable; and evert the peritoneal edges as the outside incision is closed. This latter usually may be done, if care is used, with an ordinary con-

tinuous whipover stitch, though a Lembert or mattress stitch may at times be advisable.

4. Be careful in operating to keep the skin and its edges well covered, and to follow strict asepsis in other ways, in order to prevent the introduction of bacteria onto viscera which have been in long contact with an abdominal pack, or which have in other ways been traumatized

5. Keep the patient's water balance properly maintained

6. Avoid the introduction of an unnecessary quantity or size, and of unnecessarily hardened suture material. Bury the material when practical.

Experimental evidence by trauma measurement methods, indicating that sponging and packing as it is ordinarily done in abdominal operations does not alone cause adhesions, is presented

Cotton or gauze pledgets left attached to the gut within the closed abdominal cavity for 2 hours in an attempt to simulate some of the effects of the abdominal pack produced no permanent adhesions, except when bacterial contamination was present.

Cotton or gauze sponges left attached to the gut for 19 to 30 hours did not invariably produce permanent adhesions.

Cotton or gauze pledgets left for 3 days or over almost invariably produced sufficient irritation to cause permanent adhesions. Occasionally, the pledgets eroded through the gut wall. A study of Table I may illustrate the damage that can result from an injudiciously used drain.

Some evidence is produced that implanted moist cotton pledgets are less irritating to the peritoneum than gauze ones. At this time, however, the author does not consider this observation of practical value.

TABLE I

Animal Serial Number	Time Pledgets Left In	Original Reaction to Cotton	Original Reaction to Gauze	Complications	Degree of Permanent Adhesions. Cotton	Degree of Permanent Adhesions. Gauze
19	18 hrs.	x	xx	Died 18 hrs. cause unknown	N.G.	N.G.
14	19 hrs.	o	x	o	o	x
25	25 hrs.	x	x	o	o	o
15	27 hrs.	x	xx	Gut torn in removal gauze	Cotton favored	Cotton favored
24	28½ hrs	x	x	o	o	o
13	29 hrs.	o	o	Killed		
28	30 hrs.	x	xxx	Gut torn in removal gauze	Cotton favored	Cotton favored
					xxxx	xxxx
16	3 days	x	xx	o	x	xx
18	3 days	x	xx	Died 3 days intestinal obstruction	N.G.	N.G.
29	4 days	xx	xx	o	xxx	xx
30	4 days	x	x	o	xx	xx
37	5 days	x	None used	o	xx	
38	5 days	x	None used	o	o	
39	5 days	x	None used	o	xx	
40	5 days	None used	xxx	Gut torn in removal gauze	Cotton favored	Cotton favored
41	5 days	None used	xx	o		xx
42	5 days	None used	xxx	Some contamination	Cotton favored	xxx
43	5 days	None used	xx	o		xx
34	7 days	xx	xx	o	xx	xx
32	7 days	xx	xx	Hole torn in gut by adhesion	N.G.	N.G.
27	8 days	xxx	xxx	None	xxx	xxx
33	10 days	xxx	xxx	Gut torn in removal cotton	Gauze favored	Gauze favored
35	13 days	xxx	xxx	Hole torn in gut by adhesion	N.G.	N.G.
31	16 days	xx	xxx	Gut torn in removal gauze	Cotton favored	Cotton favored
21	?	x	xx	Gut torn in removal gauze	Cotton favored	Cotton favored

(American Journal of Surgery, 39-41, Jan., 1938)

Though the author has produced evidence that sponging and packing alone will not produce adhesions, he thinks it may be possible that sufficient irritation may come from these procedures, particularly that of packing, to enhance adhesion formation by bacteria. He believes, with other investigators, that bacteria introduced into the abdominal cavity at operation may sometimes cause adhesions, and that great care should be used to minimize their introduction.

Other measures which are prophylactic against adhesion formation are briefly listed

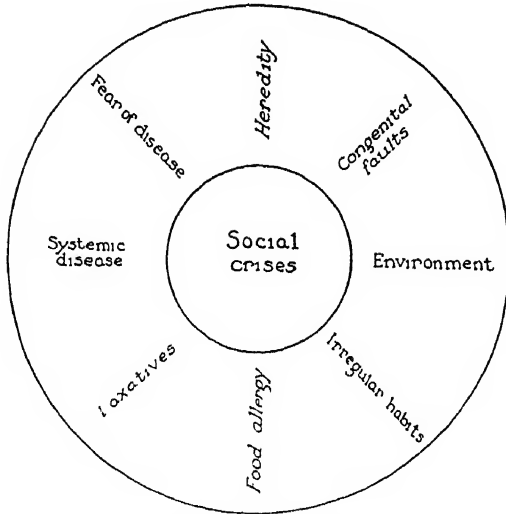
Data regarding the use of a cotton base sponge is presented; and it is felt that hospitals concerned with strict economy might profitably seek the co-operation of their surgical staffs in its use.

COLON

Functional or Sociologic Disorders

Persons who have a functional disorder of the colon which may have been excited by social conditions describe symptoms which they believe arise in the colon, but when the colon is examined it is found to be free of physical changes which are indicative of organic disease. E. G. Wakefield and Charles W. Mayo⁹ point out that the disorder is manifested by irregularities of defecation and apparent alteration in the absorptive and secretory functions of the colon. It frequently is associated with abdominal discomfort, pain and often with mucus in the feces and subjective abdominal distention. Variations in these symptoms are the rule. However, the patient will rarely admit of periods without some

"suffering." Changes in symptoms may be related to changes in the qualities of mucus present in the feces. Alternating periods of constipation and diarrhea are not uncommon, but the outstanding symptom usually is either diarrhea or a constipation.



Diagrammatic representation of etiology of sociologic diseases of the colon (Courtesy, Journal American Medical Association, October 29, 1938)

Surgical treatment of the functional disorders of the colon, as an adjunct to rational therapy, is definitely contraindicated. When operation is performed in the absence of organic disease, it denotes an error in surgical judgment. There is much misconception relative to the importance of ptosis as an important factor in these disorders, and surgical procedures infrequently have not been advocated and performed with varying degrees of success, depending rather on the honesty of the surgeon than on the necessity of the procedure. Success of operation, in other words, has not been noteworthy.

A patient with a functional disorder of the colon may require surgical intervention for other abdominal disease, and fine differential diagnostic judgment is

often required in such cases. When it is necessary to operate under these circumstances, it is important to make sure that the patient understands that the proposed operation is not intended to alleviate those abdominal symptoms referable to the functional disease. Surgical advice, therefore, in functional diseases of the colon consists, for the most part, of advice against surgical intervention.

It is evident that the cure of these functional disorders is not to be sought merely in certain dietary rearrangements but in attempts to control scientifically the adverse social conditions. This is not always possible because many patients, from the standpoint of heredity, are incapable of meeting the exigencies of life and are therefore socially pathologic. In order to eliminate these disorders, the defects in education, government, religion, morality, philanthropy and even physical heredity have to be corrected. This ideal may be approached when there is a scientific understanding of the conditions necessary for normal social life. This ideal will never be attained by treating these patients for "colitis." It is only necessary to say in conclusion that the wisest measures should be directed toward the reclaiming of those who have already been caught in their meshes.

Volvulus of the Cecocolon

Torsion or volvulus of the cecum and ascending colon is an infrequent and rare cause of intestinal obstruction. M Weinstein¹⁰ states that the disease is most common in the third and fourth decades of life, and the sex ratio is approximately 3 males to 1 female. Volvulus of the cecocolon occurs only in the presence of a defect in development, namely a congenitally long mesentery of the cecum, produced by an abnormal rotation of the cecum from left to right. In addition to an abnormally long mesentery, the pro-

duction of volvulus requires a fixed point about which the intestine can rotate. This point may be the mesentery of the small intestine, or a congenital or inflammatory band resulting from a previous operation. The first case herewith reported had a chronic adhesive appendicitis with its tip fixed to the posterior parietes by many

days' duration preceded this onset. One of the patients had mild attacks for a period of 17 years, while the other was free from such disturbances. Evidently, where there is megacolon and great mobility of the cecocolon, the patient experiences so-called chronic attacks. The pain of volvulus is intermittent and

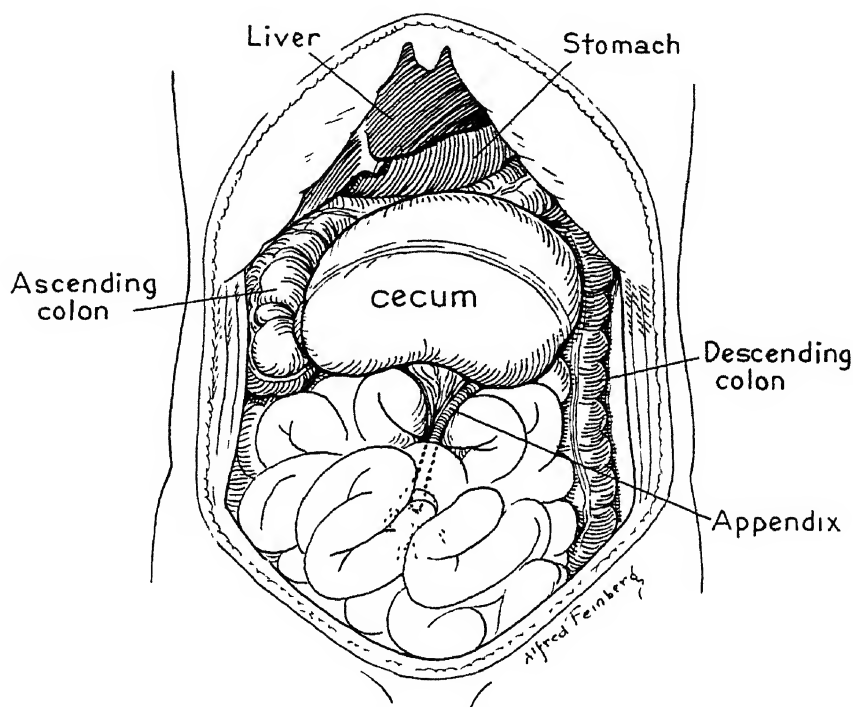


Fig 11—Case 1. Drawing representing the findings at operation. A distended mobile cecum was rotated around 2 fixed points, one being the appendix, bound down at its tip by numerous adhesions, and the other the ascending colon. Note the obstruction of the small intestine by the cord-like appendix. (*Annals of Surg.* 107: 248 (Feb.) 1938)

firm adhesions. As a fixed point, this was the contributing cause of the obstruction.

Symptoms and Diagnosis—Volvulus of the cecum presents the clinical picture of intestinal obstruction, and, because of its rarity, is seldom diagnosed except at operation or at autopsy. Pain initiates an acute attack, and, because of the severity, is unlike any abdominal pain previously experienced by the patient. In both of the cases herewith reported, constipation of 2 or 3

cramp-like in character, caused by the peristaltic and distending phenomena of hollow viscera, as in any other type of acute intestinal obstruction. Like most acute abdominal conditions, a patient's symptoms may be vague and indefinite, simulating the more frequently observed visceral inflammations such as gall-bladder disease, as reported by Sarles. Great abdominal distention accompanies the attack, and promptly disappears if the obstruction should be relieved spontaneously. This is followed by the evacuation

of a copious foul stool and gas. A large tympanitic mass may be observed in some cases, but the location varies with the amount of mobility of the cecum, as well as its location. Vomiting, of course, is a usual accompaniment, and, inasmuch as the obstruction is at a low point in the intestinal tract, signs of toxemia are delayed. The elevation of blood urea,

more extensive studies and observations were possible, further abnormalities would probably be discovered. Chalfant's case demonstrated a mammalian bicornate uterus in addition to the cecal anomaly.

Treatment—For those patients who come to operation, 1 of 3 procedures should be considered: (1) *Untwisting*

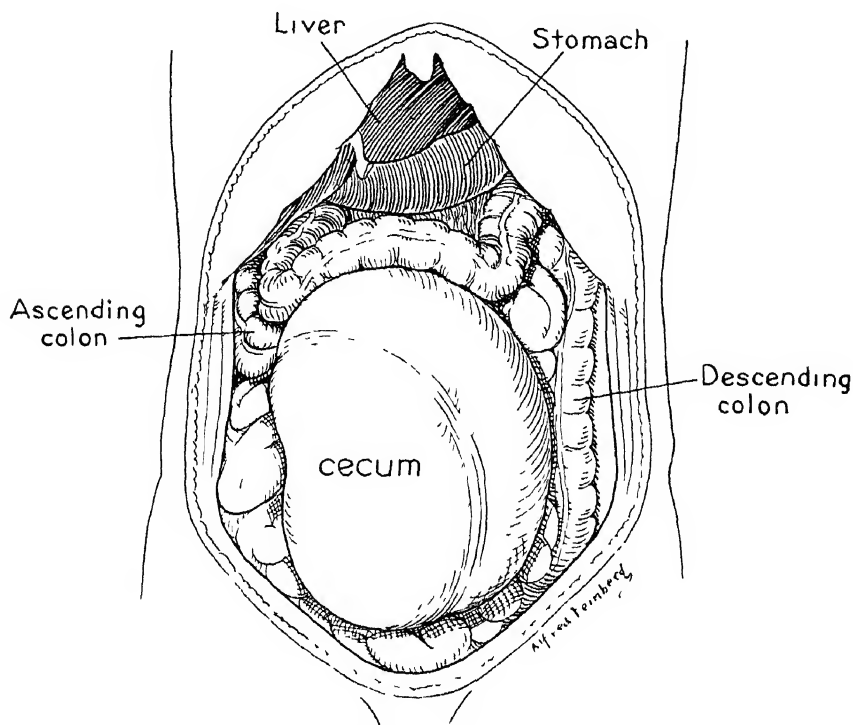


Fig. 12—Case 2. Drawing representing the findings at operation. An enormously distended cecum, the result of volvulus of the cecocolon, occupied a large part of the abdominal cavity (Annals of Surgery 107: 248 (Feb.) 1938.)

decrease in plasma chlorides, and increased combining power of the blood for carbon dioxide obtain with regularity only in high intestinal obstructions. Viable bowel has little absorptive power of toxins. Enemata and cathartics are of no avail during an attack. The patient's only relief is obtained by operation, with mechanical detorsion of the volvulus.

Like all congenital abnormalities, volvulus of the cecum may be accompanied by other defects. Case 2 also presented an elevation of the right diaphragm. If

of the volvulus with the separation of adhesive bands that may be present, (2) a *plastic operation* to avoid recurrence, or (3) *resection* of the involved colon.

1. The simplest method, of course, is untwisting the obstructed loop. This method may not be applicable in patients with extreme distention of the colon, because slight trauma may rupture and tear the already thinned-out cecal wall. One may find omental or inflammatory bands completing the obstruction and these should be severed. If, as in Case 2, an

adherent appendix helps to precipitate the obstruction, then this must be released and removed. As unsatisfactory as simple mechanical untwisting may seem to the surgeon for permanent relief, yet if the condition of the patient does not warrant further surgery, one must be content with this procedure.

2. Cecostomy and suture of the untwisted cecum to the abdominal wall constitutes the operation of choice. The replacement of the greatly distended cecal segment may be facilitated by a radical reduction in its size, following which, fixation bands to the posterior abdominal wall may be more easily visualized, and the exact status of the vascular disturbance ascertained since the enormous distention may be caused by anaerobic gas formation, as previously mentioned, and not by fluid content in the lumen, perforation by trocar and cannula is a relatively safe procedure. Through this opening into the collapsed cecum, a Pezzer catheter No. 30 or 32 is inserted, fixed to the margin by catgut, and inverted by a purse-string suture. In closing the abdominal wound, several interrupted sutures include the cecal wall above and below the cecostomy opening, thus fixing the cecum to be abdominal wall in the corrected position. After the resumption of normal bowel evacuations, the cecostomy gradually ceases to function and the Pezzer catheter may be removed. The opening eventually closes without any further surgical procedure.

3. Resection of the cecum with adjacent involved viscera is reserved only for far advanced cases. Accompanying this late stage volvulus, one usually finds gangrenous areas of the intestinal wall with necrosis. The bowel is so devitalized that contamination of the adjacent peritoneal surface is usually present. Even slight handling and manipulation may be disastrous. The only recourse is

rapid resection of the gangrenous portion, delivery of the 2 open loops of gut outside the abdomen with or without tubes. Later, if the patient survives, an attempt may be made to effect continuity and peritonealization. However, this radical procedure results in a mortality of 50 per cent, according to Jacobsen.

Cecocolon volvulus is a form of intestinal obstruction of infrequent occurrence, depending for its mechanism upon a mobile cecum with an abnormally long mesentery.

Abortive attacks of torsion may precede a severe acute attack, and are usually subsequent to periods of constipation.

Rapid and extensive gas formation in the involved loop is probably caused by the action of colonic anaerobes growing in an oxygen deficient region.

Other congenital anomalies frequently accompany this condition, and should be searched for. An elevation of the right diaphragm was discovered in 1 of the cases herewith reported.

The procedure of choice, if operated upon soon enough, is *detorsion*, *cecostomy*, and *cecopexy*.

Two cases with cecocolon volvulus are herewith reported, whose course and findings closely resemble those previously recorded in the literature.

Interposition of Colon During Childhood

Interposition of the colon has been repeatedly observed in adults but has not received attention in the pediatric literature. A Windorfer¹¹ demonstrates that this disorder has theoretical and practical interest during childhood. The disorder consists in a misplacement of the colon between the liver and the diaphragm. The case reported concerns a girl, aged 8. The child was subjected to a pulmonary roentgenoscopy because a tuberculin test had been positive. The

child had been unsuccessfully treated for abdominal pains, which dated back more than 4 years. The first roentgenogram of the lung disclosed an accumulation of air under the right diaphragmatic arch. Repeated roentgenography revealed that this air space was comparatively large. The hepatic resistance could not be felt on palpation. Roentgenography following a contrast meal finally disclosed the interposition of the colon between the liver and the diaphragm. It was decided that this condition was responsible for the abdominal pains, from which the child had suffered for years. In the differential diagnosis of this disorder, conditions like umbilical colic, appendicitis, helminthiasis and ileus have to be considered. The treatment is rather unsatisfactory. The acute attack requires the use of spasmolytics and heat. Aside from restricting bloating foods and those with large amounts of cellulose, dietetic measures are unnecessary. The muscles, particularly those of the abdomen and the back, should be strengthened by suitable gymnastics.

Incidence of Diseases of the Colon

Observations on the diagnosis and treatment of colonic disease, made during the study of 1574 cases of diverticulosis, colitis, dysentery and carcinoma, excluding the rectum, has been made by E. Spriggs.¹²

The value of sigmoidoscopy and x-ray examination is stressed. Ptoxis of the colon is said not to be related to constipation, but the real disorder is the general loss of nervous and physical tone. In 10 per cent of the patients the complaint of constipation was not justified. Of 1000 patients in whom a delay was demonstrated, one-half of the colon was involved; in one-third of these patients, the sigmoid and rectum were involved, and in 11 per cent the rectum only. Nearly

25 per cent of the patients were unaware that they were constipated. Failure of defecation is not usually due to weakness or paralysis of the bowel muscle, but to undue drying and hardening of the feces and the absence of normal stimulus, or to irritation or pain of some local lesion. Treatment should be directed toward the restoration of normal conditions. The diagnosis of intestinal autointoxication is to be regarded with suspicion, as the true condition is usually found to be some organic disease.

An incidence of redundancy of the sigmoid, amounting to 3 per cent, was observed. It is suggested that the deficient shortening on evacuation during the years of constipation may tend to cause elongations of the bowel.

Mucomembranous colitis has become less common recently, and this may be due to the widespread teaching of the harm of daily purgation, and the beneficial effects of better balanced diets. In ulcerative colitis, most of the bacteriological methods of treatment have proved disappointing.

A prediverticular state has been observed in 132 of 564 consecutive cases of diverticulosis. This appears to be due to local spasm of groups of muscular fibers. Observations suggest that there is some preceding process, probably inflammatory, which determines the site at which pouches will develop. Diverticula may remain quiescent for years, or until the end of life, but occasionally the necks become inflamed and inflammation spreads to the bowel wall. Pain, bowel irregularity, and backache may result. Operative intervention is not very often necessary, because medical measures frequently result in a remission.

The average age of 64 patients with carcinoma of the colon was 62 years. The sex incidence was 3 men to 1 woman.

According to the mode of onset, distribution was made as follows:

1. Bowel disturbance, 36 cases.
2. Pain, 17 cases.
3. Discomfort in upper abdomen or nausea, 11 cases.
4. Blood in the stool, 11 cases.

Diverticulitis and carcinoma were found together in 6 patients. The tumor was excised in 13 patients, and the operation was successful in 8, 2 of whom were living 10 years later.

Congenital Megacolon

A case of Hirschsprung's disease is discussed by R. A. Bate,¹³ in which the symptoms of congenital hypothyroidism were so definite that it is believed that the proved pathologic changes of the 2 diseases justify the assumption that Hirschsprung's disease is caused by congenital hypothyroidism in probably all cases and is therefore not a disease but a subsyndrome of hypothyroidism.

Treatment—In the treatment of congenital megacolon, A. Friedell¹⁴ suggests daily *irrigations* with *physiologic solution of sodium chloride* at 115° F (46.1° C). In 3 cases, treatment consisted of irrigation through a rectal instrument which permitted a controlled inflow and outflow. The treatment lasted from 30 to 90 minutes at first, depending on the response of the patient, but never less than 20 minutes. Several gallons of solution were used at one time. The solution was prepared at the bedside by dissolving the required amount of salt in a gallon of hot water. The irrigations were given slowly to avoid distention. In a few days the patients showed signs of improvement. Hurry or rough handling will frustrate all efforts and aggravate the condition. While in the 3 cases discussed, normal intestinal function has been established, no claim can be made that all patients with megacolon can be

cured. No damage should be done by trying this method first, and those ultimately requiring a sympathectomy will be better prepared by such irrigations.

Chronic Ulcerative Colitis

During the years 1925 to 1931 inclusive, J. A. Bargen and his colleagues¹⁵ observed 73 patients who had tuberculous ileocolitis at the Mayo Clinic, approximately 500 who had amebic colitis, 129 who had ulcerative colitis of undetermined etiology and 871 who had thromboulcerative colitis (of bacterial origin). A statistical study of the records of the 871 patients who had thromboulcerative colitis, followed from 7 to 14 years after the first observation, shows that the predisposing factors and those affecting relapses of the disease are: Infection of the upper part of the respiratory tract, disease of childhood, dietary indiscretion, physical and mental fatigue, rectal or abdominal surgery, trauma, drastic catharsis, foci of infection with sepsis, exposure, dysentery epidemics and pregnancy. This disease may begin in an insidious manner. Again it may come on suddenly as a violent diarrhea without toxic symptoms or it may start in a fulminating fashion associated with marked toxemia, fever and all the concomitants of a severe septic process. The major complications and sequelae of thromboulcerative colitis include polyposis, stricture, perianal abscess-fistula, arthritis, erythema nodosum, pyoderma gangrenosa, perforation, hepatic abscess, carcinoma, phlebitis, iritis, deafness, splenomegaly, nephritis, psychosis, massive hemorrhage, endocarditis and renal stones. There is no special time of year in which the disease begins, but more of the cases had their onset in January, February or July than in the other months of the year. The progress of the invasion from the rectum toward the

cecum is indicative of its destructive nature. The mortality (at the time of inquiry 19.3 and 12.9 per cent, male and female, respectively) associated with this destructive infection emphasizes its serious nature. Surgical intervention in this disease should be limited to complications and sequelae. Some of these demand wisely chosen surgical measures, both from the standpoint of the time of their application and from that of the lesion present. A person with thromboulcerative colitis presents a poor surgical risk if a surgical attempt must be made to relieve another intercurrent abdominal pathologic condition. Complete relief of all symptoms and signs of intestinal pathologic change occur frequently enough to make it urgent that a well-ordered regimen be followed without deviation by these patients for months and years.

Treatment—J. K. Ferguson and his associates¹⁶ have treated 5 cases of ulcerative colitis by *artificial fever*, for the production of which they used the Kettering hypertherm. Their method of treatment consisted of 2½ to 3 hours of fever between 104° and 105° F (40° and 40.5° C) (rectal) 3 times a week. The number of treatments varied between 7 and 17, the average being 12 per patient. Each patient responded favorably to fever therapy, the clinical improvement preceded the improvement in the proctoscopic appearance. In most cases, after 3 or 4 treatments the number of stools was markedly reduced and bleeding and tenesmus were less. The patients' appetites improved and their weights began to increase. In spite of the clinical improvement, fever treatments were continued until the proctoscopic appearance, also had improved, except in 1 patient, who refused to have more than 7 fever treatments. In this patient the appearance of the intestine on

proctoscopic examination continued to improve, in spite of the fact that fever treatments were not continued. The use of artificial fever in the treatment of ulcerative colitis is not regarded as a treatment that will produce a permanent cure.

A method of *topical application of cod-liver oil* to the mucosa of the descending colon, sigmoid and rectum has been devised by I. A. Manville¹⁷. The apparatus is composed of an ordinary paint gun as employed in the application of paint by the spray method. The only difference is that the nozzle is specially designed so that the tip will barely protrude beyond the end of a sigmoidoscope. The air pressure is adjusted by the use of an air pressure reduction gauge so that it is barely sufficient to deliver a spray at the tip of the nozzle. The preliminary care of the patient is similar to that commonly employed for a proctoscopic or sigmoidoscopic examination with the exception that in addition a cleansing enema is used. The sigmoidoscope is inserted full length, the nozzle of the spray gun is then placed in position and the pressure is released. The entire apparatus is slowly withdrawn, thus leaving a thin coat of cod-liver oil applied directly to the mucosa. If necessary an oil (½ oz. or 15 cc) retention enema may be used at night. This method of treatment of ulcerative colitis substantiates the results given by Spiegel and the technic described is believed to be better. The few patients who have been treated have been distinctly benefited.

Regional Ileitis and Ulcerative Colitis—The etiological aspects of regional ileitis with those of 3 cases of ulcerative colitis with lymphogranuloma of the large intestine are compared by E. S. Stafford¹⁸. The clinical history in each case is not unlike that of a case of regional ileitis, the chief differential

point being the presence of a positive Frei test. Under the microscope, in the last of these 3, the typical lymphogranulomatous lesion is present and easily differentiated from the nonspecific lesion of regional ileitis. The microscopic appearance of the lesions in the first 2 cases of lymphogranuloma is not strikingly different from that of regional ileitis. In no case of regional ileitis were any tubercle-like structures found. The presence of a small foreign body in the third case cited is no doubt secondary to ulceration of the mucosa. In lymphogranuloma, intestinal lesions may occur anywhere in the large intestine. No case has been observed in the Johns Hopkins Hospital, however, in which ulceration due to lymphogranuloma has been found in the small intestine. In the present series of 10 cases of regional ileitis the Frei test, when carried out, was negative.

The intestinal lesions due to the virus of lymphogranuloma are confined to the large intestine, whereas in regional ileitis the lesions are located in the small intestine. Many cases have recently been reported in which lesions were found simultaneously in the small and large intestines. These should be reconsidered, in the light of the possibility of discovering lymphogranuloma. The clinical features in the 2 types of cases are similar. The many points of similarity in the clinical course and, to a lesser extent, in the pathologic picture between lymphogranuloma of the intestine and regional ileitis suggest that the lesions of the latter are also produced by a virus infection. Further work with material from regional ileitis must be done to settle this point. Tuberculosis and amebiasis have both been adequately disposed of as possible etiologic factors by earlier writers on this subject.

Tumor-like inflammatory masses in the intestine occur most frequently in the

lower ileum, but a few reports indicate that other parts of the gastrointestinal tract have been affected. Isolated involvement of part of the colon is distinctly unusual and for this reason T. G. I. James¹⁹ reports his case of chronic regional colitis.

The patient, a male 19 years of age, complained of paroxysmal, colicky abdominal pains of 7 weeks' duration. He had passed bright red blood in the stools and had lost considerable weight. Upon examination, tenderness was elicited in the left side of the abdomen where a firm, slightly movable mass could be felt. X-ray examination with a barium enema revealed a narrowing of the gut, which involved the distal part of the transverse colon, the whole of the descending and iliac portions, and the upper part of the pelvic colon. At operation, a small amount of serous fluid was found in the peritoneal cavity. The large gut from the distal part of the transverse portion to the upper part of the pelvic colon was firm and rubbery, and 2 or 3 times the normal size. There was a sharp demarcation between the unaffected and the diseased portion of the bowel. Resection of the affected portion of the large gut was performed. The specimen removed measured 15 inches in length. The lumen was extremely narrow, admitting only a medium sized probe, the gut wall was 2 cm in thickness, and the mucous membrane showed numerous superficial ulcers. Convalescence was uneventful.

The clinical features emphasized in this case are abdominal pain, loss of weight, low-grade fever, anemia, diarrhea, and a palpable mass in the abdomen. The radiological findings were similar to those described by Kantor and designated as the "string sign." Pathologically, the changes are those of a nonspecific granulomatous inflammation associated with ulceration of the mucosa and hyper-

plastic changes involving all the layers of the gut. The *treatment* indicated is **resection** of the involved section of gut. A 2-stage operation may be necessary if obstruction exists.

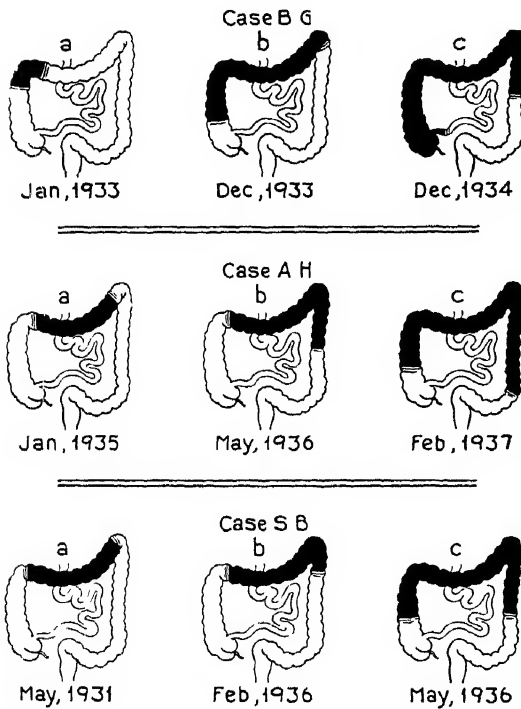


Fig. 13—Spread of the lesion. Progressive course of life history of regional colitis (diagrammatic) (J. A. M. A., Jan. 1, 1938.)

Right-Sided (Regional) Colitis

Right-sided (regional) colitis is a disease that has its origin somewhere in the colon on the right side. It constitutes about 10 per cent of the cases of colitis, is progressive, somewhat less severe, and shows fewer spontaneous cures than the left-sided type. The disease, which may begin in any part of the colon on the right side, tends to spread upward and downward, and is retarded for various periods at the hepatic, splenic, and sigmoid flexures.

Medical treatment in the hands of B. B. Crohn and A. A. Berg²⁰ has been disappointing and they believe that **operation** is indicated in all intractable

cases. Since the operation that is utilized depends entirely upon an anastomosis with a healthy sigmoid, it becomes absolutely imperative to intervene surgically whenever the lesion shows a tendency to invade the pelvic colon; this segment makes surgery possible.

The operative procedure is divided into 2 or 3 stages. In the first stage, healthy ileum is anastomosed to the sigmoid. The sigmoid is divided in a healthy area, and its distal end is turned in. The diseased proximal segment is brought out at the upper end of the operative wound as a colostomy. This permits the fecal stream to be sidetracked through entirely normal tissue and the infected contents of the involved colon to be discharged out of the body. Following a period during which the patient is permitted to build up his strength, a second operation is done, at which time the diseased colon is removed entirely. Occa-

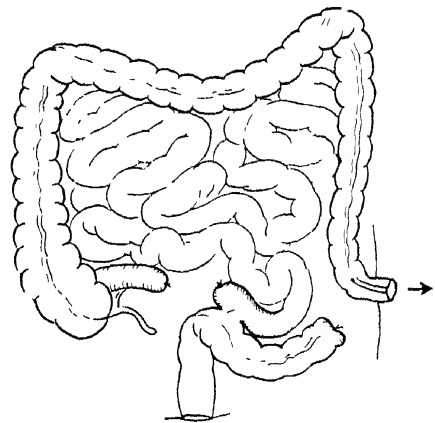


Fig. 14—Implantation of proximal end of ileum into the lower sigmoid. Complete division of 2 upper ends of sigmoid. Closure of the distal end of sigmoid. Establishment of artificial anus in proximal end of sigmoid (J. A. M. A., Jan. 1, 1938.)

sionally the latter operation has to be done in 2 stages.

As performed, the operation offers these advantages: (1) There is absence of shock, (2) the suture lines are guarded against infection since the infected con-

tents are discharged outside; (3) extirpation of the colon is made possible even in debilitated individuals, and (4) the continuity of the alimentary tract is maintained without a permanent stoma in the nature either of an ileostomy or of a colostomy.

Diverticulitis of Colon

Diverticula occur in all portions of the gastrointestinal tract from the esophagus to the rectum, but most frequently are found in the sigmoid colon. No adequate etiological explanation has been offered. It would seem, however, that from some unknown cause, probably congenital, a weakness exists in the intestinal coats and by reason of this a pouching of the coats takes place when any undue pressure arises.

F. W. Rankin and A. E. Grimes²¹ state that about 5 per cent of cases examined by barium enema will show diverticula, the vast majority of patients are beyond 40 years of age, and sex plays no part. The presence of diverticula causing no complaints is described as diverticulosis. With the onset of inflammatory changes the condition is designated as diverticulitis. Acute, subacute and chronic diverticulitis are considered to be fundamentally medical problems, and the complications of abscess formation, partial obstruction, massive hemorrhage, external or internal fistula, and associated malignancy essentially surgical.

Uncomplicated cases usually manifest themselves by some alteration in bowel habit, frequently constipation, alternating with occasional diarrhea. There is an associated variable degree of pain ranging from heaviness, fullness, or soreness to severe cramps, bleeding is rarely profuse and nausea, vomiting palpable mass, and stools of reduced caliber will be dependent upon the degree of ob-

struction present. Proctoscopic examination is often of great aid but the most accurate information is obtained from reliable roentgenological studies. The principal findings are the rounded knob-like projections from the lumen of the colon, spasm, and hypermotility. The relationship of cancer and diverticulitis is only coincidental and it must be remembered that diverticulitis with tumefaction may mimic cancer in its gross appearance. The diagnosis of the acute group perforating into the peritoneal cavity without abscess formation is quite difficult unless the previous presence of the diverticula is known. The condition is most frequently diagnosed as acute appendicitis or ruptured duodenal ulcer.

The type of surgical treatment indicated is determined by the nature of the complication requiring surgery. A single perforated diverticulum should be closed, drains packed around the involved area and a *temporary colostomy* done. *Resection* may be indicated in the perforating type which walls off, and forms an abscess which burrows to beneath the anterior abdominal wall, requires incision and establishes a fistula. Where obstruction is the main factor where a large immobile mass is imbedded in the pelvis, a colostomy allowed to remain open for 6 to 12 months, during which time the Elliot treatment can be given, seems the best procedure to follow. If a vesical fistula is present, primary resection is not advisable. There should first be a colostomy and bladder treatments to clear up infection and inflammatory reaction.

Perforating Lesions of the Colon

The Roentgenological Diagnosis— The treatment and prognosis in tumefactive lesions of the large intestine are conditioned primarily on whether they are of neoplastic or of nonneoplastic na-

ture The lesions of the rectum and lower sigmoid within reach of the proctoscope are left out of consideration here for the reason that no less direct diagnostic method could conceivably be more accurate and reliable than the competently performed proctoscopic examination in the diagnosis of these lesions.

C. F. Dixon and H. M. Weber²² show that the roentgenological examination can be made to reveal the presence of any tumefactive lesion of the large intestine, at least as early in its development as it is able to manifest itself by clinical signs and symptoms. Such lesions are exhibited roentgenologically by producing what is called a filling defect, which may be defined as a constant, persistent subtraction from the normal contour.

Carcinoma of the large intestine is manifested roentgenologically by signs so consistently distinctive that they are considered to be only slightly less pathognomonic than the gross morphological picture itself

The typical neoplastic filling defect is always confined to a relatively short intestinal segment, and describes a more or less marked, but relatively pervious, narrowing of the lumen

Different histological and gross morphological types of carcinoma present different intraluminal relief patterns, but the normal relief is always entirely obliterated. Polypoid carcinoma produces a marginal filling defect only when ulcerated, in which case the relief pattern reflects its saucer-like form; but again the granular amorphous character of the surface is apparent, broken irregularly by elevations corresponding to the excrescences of carcinomatous substance on the surface. Invariably apparent, however, and the most telltale feature of the neoplastic relief pattern is the abruptness with which it is delimited from the

uninvolved mucosa proximally and distally contiguous to it.

The typical nonneoplastic filling defect is best defined as one in which the pathognomonic evidences of true neoplasm are lacking. It is essentially a constriction of the lumen, embracing only a part of 1 of the divisions of the large intestine, but it usually is a longer defect than the 1 associated with neoplasm. Inflammatory disease in general is progressive and to a certain extent self-limited, and the gross morphological as well as roentgenological appears depend largely on the stage of development at which the lesion is observed.

The tuberculous, amebic, and the streptococcic granulomas are the principal examples of this group of inflammatory tumefactions. Combined involvement of the ileum and cecum is commonly seen when an inflammatory tumor involves this region, a phenomenon never seen with neoplasm unless perforation has taken place. All of these morphological features are reflected faithfully in the roentgenological picture

When the roentgenological examination has demonstrated that a tumefactive lesion is present, and has offered its dependable conclusions about the neoplastic or nonneoplastic nature of the tumor, it has made about as great a contribution to the final diagnosis as may be expected of it. There are no fundamentally reliable roentgenological signs by which the various etiological types of inflammatory tumor can be distinguished from each other and the final diagnosis often, if not usually, reads "nonneoplastic tumefaction of indeterminate etiology"

The filling defect produced by neoplastic lesions which have perforated or which have otherwise been complicated by infection looks much more like the filling defect of the inflammatory tumors than like that of the true neoplasms. Dia-

critical roentgenological signs of the original lesion are not, however, obliterated beyond the point where roentgenological methods fail to reveal them, and it is here that familiarity with the internal relief of the neoplastic lesion is of particular value.

The fundamental importance of obtaining adequate visualization of the entire extent of the filling defect, and of making a most careful study of the structural detail of its internal relief, should be obvious. It may be said that a dependable roentgenological diagnosis of "neoplasm and perforation" can be made whenever it occurs, and to confuse the condition consistently with the non-neoplastic tumefactions is to fail to exact the full diagnostic yield of the roentgenological examination.

Surgical Considerations—Clinical signs and symptoms, although more indirect, may in certain instances be all but pathognomonic, but they are always of great value. Barger and Dixon have described certain features of perforating neoplasm which have been of great diagnostic utility. One of these is the character of the reaction following the preoperative intraperitoneal administration of a vaccine prepared from bacillus coli and streptococci. The normal reaction in the presence of nonperforating lesions of the colon is an elevation of the temperature of the body from normal to 101° to 103° F (38.3° to 39.5° C) within 10 to 12 hours. A similar reaction seems to be evoked by metastatic lesions in distant organs.

The coexistence of infection and neoplasm entails difficulties not encountered if the lesion is purely neoplastic or purely inflammatory. Whether complicated by infection or not, neoplastic lesions demand radical treatment, yet the very presence of infection may seriously im-

pede the institution of the more radical surgical procedures indicated.

The surgical treatment of diverticulitis provides an exemplification of these principles. In many instances this condition may be treated satisfactorily without surgical intervention. A combination of a *low-residue dietary regimen*, methods of applying *local heat*, and *anti-spasmodic drugs* administered liberally, often effects subsidence of the inflammatory process within reasonable limits of time.

The formation of pericolic abscess with and without extension to adjacent pelvic viscera, especially to the urinary bladder, with the development of sigmoidovesical fistula, are among the more frequent complications of diverticulitis. Fecal fistula may develop following drainage and necessitate surgical treatment such as segmental resection. Spontaneous closure of the fistula may follow establishment of a temporary colonic stoma without direct attack on the fistula itself. After closure of the fistula the continuity of the bowel can be re-established. Surgical treatment is usually necessary to bring about closure of a sigmoidovesical fistula.

In the surgical treatment of intestinal tumefactions, it seems worth while to remark briefly about the use of *intraperitoneal vaccine* preoperatively. Accumulating experience seems to indicate that by this means the mortality from intestinal surgery is appreciably reduced. Intraperitoneal vaccination is therefore recommended. If gross examination occurs during an operation on the intestine, the insult to the peritoneum may be too great for it to overcome. The authors' observations lead to the belief that the death rate following removal of perforated lesions of the intestine has also been reduced as a result of these serums.

Experience also indicates that the operative mortality can be reduced still more if some kind of short-circuiting operation is carried out before the diseased segment of intestine is resected. Short-circuiting or sidetracking procedures are of particular advantage if the perforating lesion is situated well above the sigmoid colon. As a rule such operations are not employable for lesions of the sigmoid or lower pelvic colon, because, if the greatest care is not exercised, contamination will occur when the lesion is subsequently removed.

If feasible, perforating lesions of the colon are most satisfactorily managed by using a short-circuiting procedure as the first stage of the operation. The use of anaerobic serum is recommended only because some of the fatal peritoneal infections following operations on the colon have, with apparent justification, been attributed to anaerobic microorganisms.

Submucous Lipomas of the Colon and Rectum

A review of the literature by J. Pemberton and C. J. McCormack²³ revealed 113 cases of submucous lipoma of the colon and rectum. In 94 of these cases the tumor produced symptoms. Three cases in which the condition was treated successfully by operation have been added. Submucous lipomas of the colon and rectum affect chiefly women who are between 40 and 60 years of age. The tumors are found in the cecum, ascending colon, and sigmoid flexure, in the order named. The condition is rarely diagnosed preoperatively; the most common diagnosis is carcinoma and acute appendicitis. The symptoms are those of intestinal obstruction, and the average duration of symptoms is 41.5 months. The treatment is **surgical removal** in 1 stage, if possible, or by means of graded procedures.

Endometriosis of the Colon and Rectum with Intestinal Obstruction

As the symptomatology of cancer and endometriosis of the large intestines may be similar, it is very important to be able to differentiate them, preferably before, but certainly at operation. R. B. Cattell²⁴ states that it is only thus that one can avoid, in cases of endometrial implants of the colon and rectum, the more radical resections that are essential when dealing with malignancy.

Long-standing endometriosis may involve the sigmoid and rectum to the extent of producing gastrointestinal symptoms and intestinal obstruction. Intestinal symptoms due to this cause were present in 17 (16.3 per cent) patients of the series of 104 patients with endometriosis.

The diagnosis seldom is made preoperatively, but this condition should be suspected when the obstruction is long-standing and worse at the time of menstruation, when there are associated pelvic findings, and when the local lesion on examination by the sigmoidoscope and barium enema is not typical of carcinoma of the colon or rectum. The condition can be recognized at operation.

The patients in this series have been divided into 3 groups. Those with rectovaginal involvement, those with diffuse involvement of the rectosigmoid and rectum, and those with discrete endometrioma of the sigmoid.

Because of the complicating intestinal involvement, the operative treatment must be directed not only to the ovaries but also to the intestinal lesions. Resection of the sigmoid was performed on 3 patients who had discrete endometrioma of the sigmoid, but resection has not been considered necessary in cases of the diffuse type. Because of the seriousness of endometriosis with intestinal involvement,

removal of the ovaries is recommended in such cases. The end results have been satisfactory in this series. Six cases are reported illustrating the different types of endometriosis of the sigmoid and rectum.

Carcinoma of the Colon

Clinical Aspects and Therapy —

H. Finsterer²⁵ is able to confirm the assertion made by Mickulicz, that carcinoma of the large bowel is relatively benign. For this reason an effort to reduce further the operative mortality is completely justified. The author operated upon 226 cases himself and these were studied for their results. The desire for early operation was not fulfilled; 24.8 per cent of the patients already had developed acute intestinal obstruction, and the remainder had had complaints on the average of about 10 months' duration. For the early recognition of the condition the most important thing is to think of the possibility of carcinoma and not to allow oneself to be steered into false conclusions by isolated symptoms of the disease that may make their appearance at the beginning. One of these symptoms is the painful inflation of the cecum and ascending colon, which even in carcinoma of the left half of the large intestine not infrequently may lead to a mistaken diagnosis of appendicitis.

The appearance of chronic constipation should be suspected as a sign of carcinoma in every person over 40 years of age. Also the colic-like pains which in many instances are most predominant in the right half of the abdomen do not always signify appendicitis. A palpable tumor is to be regarded as a late finding. As soon as the suspicion of a carcinoma arises, the practitioner must make the diagnosis certain by all the clinical methods of examination which are at his disposal. In addition to rectosigmoidoscopy

and the barium enema including the film of the emptied bowel, the contrast meal is also indicated. One must guard against the false diagnosis of "spasm." The latter is present only if the constriction in question disappears upon the administration of atropine. A negative x-ray finding should not quiet all suspicion. If the diagnosis still remains uncertain, then an *exploratory laparotomy* is indicated.

The contraindications for radical operation should not be carried too far, the extension of the carcinoma to the small intestine or its mesentery should not without further complications be a contraindication to radical operation. Furthermore, there is only a slightly higher operative mortality in patients over 60 years. In view of these considerations, the author sets the operability in his cases as wide as 79 per cent.

The *operative procedures* were divided as follows: 179 (79.2 per cent) were resections, 30 (13.2 per cent) colostomies, and 17 (7.5 per cent) enteroanastomoses. The immediate mortality following operation depends primarily upon the condition of the patient. The highest mortality, 30.2 per cent, occurred in the cases presenting acute intestinal obstruction which could be treated only by cecostomy at first. Since this procedure was carried out primarily under local anesthesia, the very low mortality of 8.3 per cent explains itself. The intestinal resection which was performed after complete emptying of the bowel was later modified with a closing of the ventral anus, so that a 3-stage resection was evolved which yielded a mortality of 13 per cent. It is only in intestinal obstruction caused by carcinoma of the right half of the large intestine that the typical marsupialization of the carcinoma is recommended. If there is no acute obstruction, then it is possible to carry out, other circumstances permitting, a 1-stage operation

in carcinoma on the right side, but in carcinoma on the left side it is practically always necessary to perform the 2-stage resection, in which the side-to-side anastomosis is employed almost exclusively. The 1-stage resection gave a mortality of 26 per cent in carcinoma of the right half of the large bowel, and a mortality of 30 per cent in carcinoma involving the left portion of the large bowel.

In stenosing carcinoma the 3-stage resection, giving a mortality of 23.3 per cent, is the method of choice. In this respect only 3 of the 7 deaths were directly related to the method of operation used. The entire series of 3-stage resections in cases with and without intestinal obstruction showed a total mortality of 18.8 per cent. In general, the local anesthesia was of the most significance in explaining this result, as it prevents intestinal atony and pulmonary complications, permits older individuals to be subjected to operation, and allows more time for the performance of the operation. General anesthesia makes rapid operation necessary and thus tends to limit the extent of the procedure. The evaluation of the end results is based upon 96 cases operated upon at least 5 years previously and in which the diagnosis was substantiated histologically. Of all of the patients in whom resection was done, 43.7 per cent, or 57.8 per cent of those discharged as cured, remained free from recurrence for more than 5 years. Of the patients with carcinoma on the right side, 51.3 per cent and of those with carcinoma on the left side, 38.9 per cent were cured.

Carcinoma of the Rectum and Rectosigmoid

The origin and spread of cancer of the rectum is outlined by C. Gordon-Watson.²⁶ There is considerable evidence to show that in the large intestine,

hyperplasia, followed by adenoma and then by carcinoma, is a common sequence of events, and it is open to doubt if an epithelial tumor in this region is ever malignant in its earliest stage. It is not unreasonable to assume that cancer does not develop in this area without evidence of prior hyperplastic changes. In its earliest stages, cancer of the rectum begins as a proliferation of epithelium, protruding to a greater or lesser extent into the lumen, whether the malignant process commences in a level portion of mucosa (if it ever does), in a patch of hyperplasia, or in a sessile or pedunculated adenoma. The surface of the growth enlarges by marginal increase, and its depth increases by infiltration. Classification of rectal cancer into "protuberant" and "ulcerating" cancers is apt to be misleading since these are not different types but different stages. No constant relationship exists between the extent of surface growth and the extent of deep infiltration.

In the condition known as polyposis intestinalis or adenomatosis, which is generally a familial disease occurring in young people, it may be stated that malignant disease invariably completes the picture in those who fail to succumb from repeated hemorrhages or who have not been saved by total colectomy.

It is only to be expected that localized adenomatosis, as distinct from diffuse adenomatosis, would show the same tendency toward transition from benignancy to malignancy, and there is abundant clinical and pathological evidence in support of this. Multiple malignant tumors of the rectum or colon are occasionally found, but they are seldom found without the coexistence of adenomas.

Numerous observations suggest that when a very early growth is found the whole area is potentially malignant, and that the removal of 1 malignant tumor

may stimulate further malignant change. If we can accept this theory, then a local removal as distinct from resection for even very early growths seems to be contraindicated. It requires some courage, however, to advise radical surgery for a small malignant adenoma. When a colostomy is carried out as a preliminary to excision of a malignant growth of the rectum, it is not uncommon to meet with adenomas in the pelvic colon, and sometimes even with an early carcinoma.

The general rule that lymphatic spread does not occur until the growth has broken through the rectal wall must be accepted. When lymphatic spread has occurred, statistics of perineal excisions show that however extensive the surgical procedure, the odds against a patient's surviving for 5 years are 5 to 1. In every case, the regional nodes lying against the deep surface of the growth or just above it are invaded in the first instance, and then invasion follows the glands along the superior hemorrhoidal vessels upward, usually in an orderly manner, to the inferior mesenteric group. In the cases of patients who are beyond the reach of surgical cure, and in whom the superior hemorrhoidal and inferior mesenteric nodes are obstructed by extensive metastases, cancer cells may be found in the middle hemorrhoidal areas. When this happens, the iliac glands ultimately become involved. There is no tendency of the lymphatic invasion to spread from the inferior mesenteric chain, against the lymphatic current, along the paracolic vessels which drain the pelvic colon. Glandular metastasis usually progresses at a slow rate, and the surgeon is encouraged to attack growths that are obviously advanced, because he knows that even though lymphatic invasion has begun there is more often than not a considerable lapse

of time before dissemination goes beyond the limit of radical excision.

It is clear from the high survival rates among early cases without lymphatic spread that venous metastasis does not often precede lymphatic invasion, but, on very rare occasions, an undetected metastasis in the liver is a factor which upsets statistics.

Diagnosis—Cancer of the rectum can be diagnosed accurately. It is usually of low malignancy, slow to metastasize, more or less accessible, and hence, amenable to surgical extirpation. P. H. T. Thorlakson and A. W. S. Hay²⁷ stress the frequency with which malignant degeneration occurs in polyps of the large bowel. The diagnosis of carcinoma in the terminal portion of the large bowel is best made by feeling and seeing the growth, but any disease which produces an ulcer, a mass, a stricture, or which is characterized by the passage of blood or mucus, must be considered in the differential diagnosis of cancer. The most difficult problem in differential diagnosis is presented by cases of diverticulitis involving the lower sigmoid, of which about 10 per cent may become malignant.

Treatment—In both rectal and rectosigmoid cancer, adequate treatment demands *complete abdominoperineal excision of the rectum* and the *lower sigmoid colon*. In complete obstruction, the primary requisite is relief of the obstruction. The authors recommend *cecostomy* in cases of complete obstruction, and *permanent inguinal colostomy* in cases which are not so severe. This is generally followed by prolonged medical care to decrease the operative risk. Prior to operation, *peritoneal vaccination* is carried out.

The essential principle of all the abdominoperineal operations includes removal of the entire anus, rectum, ischio-

rectal fat, levator ani, retrorectal tissues, mesosigmoid, and the lower colon. Nothing short of this will succeed in removing all of the structures that may conceivably be involved in the extension of the growth. This procedure, which is described in detail, was attended by an operative mortality of 11.3 per cent in 44 operated cases.

rectum can be kept dilated. Whether or not this method is more than palliative is still open to question.

Operation On a Defunctive and Distal Colon—H. Devine²⁸ describes a defunctional distal colon as one which has been completely disconnected from the alimentary canal so that it cannot be soiled in any way by even the smallest

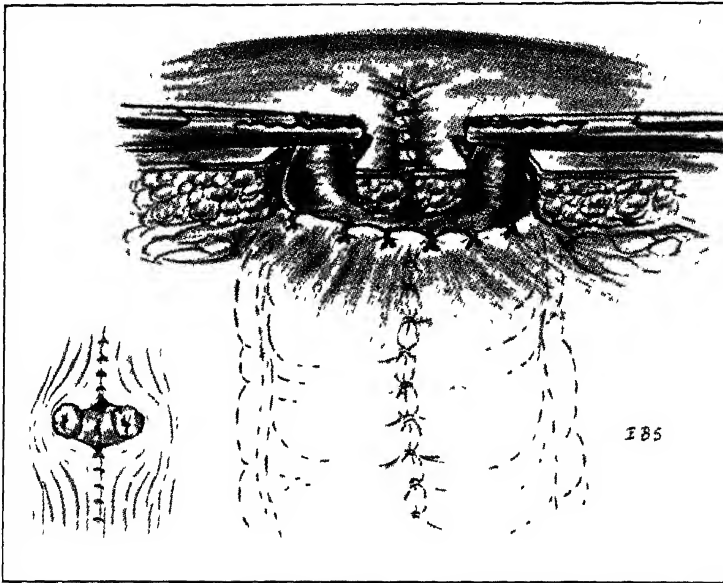


Fig. 15—Diagrammatic section to show the 2 cut ends of the bowel drawn up through the small openings by the Kocher clamps, and the main wound sutured. Inset shows position of muscle in relation to the ends of the bowel. (Surgery 3: 165, 1938.)

Perineal excision and **electrocoagulation** are reserved for early cases, or for cases complicated by various degenerative diseases which make for poor operative risks. Ten patients were treated by this method, with but 1 requiring a permanent colostomy. Under spinal anesthesia, the tumor is exposed through a bakteite proctoscope and progressively coagulated until the soft tissue is reached. Great care must be exercised to avoid injury of the adjacent tissues. It is generally necessary to divide the treatment into 2, 3, or 4 stages. If the tumor is at all extensive, a postoperative stricture always occurs, but generally the

quantity of feces, from which the fecal contents have been washed out, and which has been allowed to remain functionless until the bacterial content has been considerably reduced. The 2 important requirements in operating on the defunctioned distal colon are (1) that the operation is carried out under favorable conditions, in the absence of septic feces, functionless, collapsed and retracted colonic walls, and low bacterial content; and (2) that the wound in the intestine is allowed to heal under these conditions. The author has been able to carry out end-to-end or side-to-side anastomoses in old and debilitated cancerous

patients; to remove almost the whole of the sigmoid in inflammatory diverticular tumor, and eventually join the upper part of the sigmoid to the upper part of the rectum; to remove carcinomas of the lower end of the sigmoid, and anastomose the middle of the sigmoid to the divided rectum; to remove inflammatory

carcinoma of the sigmoid; and the surgery of innocent affections, which comprise inflammatory diverticular tumors with their complications, rectovesical fistulas, single or multiple adenoma of the sigmoid, and endometrioma of the lower part of the sigmoid or the rectosigmoid junction. Complete defunctioning of the

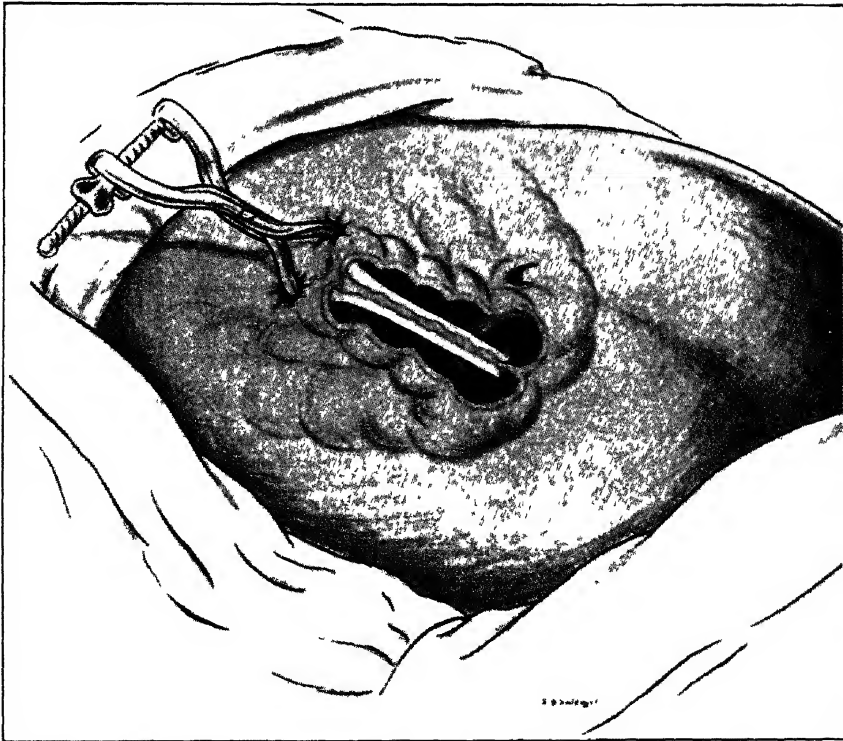


Fig 16—Diagram showing the enterotome applied. For diagrammatic purposes the abdominal wall in the drawing is considered transparent and the spur semisectional (Surgery 3 165, 1938)

diverticular tumors of the sigmoid, which by the ordinary methods of operating would be quite irremovable; to remove a series of innocent adenomas of the sigmoid by slitting it longitudinally, dissecting the adenomas out of the mucous membrane, and then closing the lumen of the bowel; and to cure the rectovesical fistula arising from diverticulitis of the sigmoid.

In the surgery of the distal colon, there are 2 main fields: The surgery of malignant conditions, the main one of which is

distal colon, especially when it is prepared by daily lavage, even if it be for the short period of a month, brings about such a profound change in the pathogenicity of the bowel contents and in the walls, that the mortality rate of operations in the carcinomatous colon is greatly reduced. The short period of defunctioning improves not only the local resistance of the patient's colonic tissues, but also the patient's general resistance.

The method of operation on the defunctioned colon involves the following:

Preliminary exploration of the abdomen. The main object of the exploration is to make an examination of the growth and of any glandular involvement with a view to its operability, and to ascertain if there is any metastatic spread of the growth, which would prohibit its radical removal.

The construction of the disconnecting anus. In regard to the disconnecting anus, there are 4 requirements: (a) That it should completely disconnect; (b) that it should be more or less continent, (c) that it should be situated well away from the area of the operation. The first is obtained by dividing the bowel and implanting the divided ends into separate openings in the abdominal wall. (Fig 15); the second, by making a small fistula-like anus at the beginning of the transverse colon with an opening so small that it can be easily occluded, the third, by combining the small fistulous anus with a third, by combining the small fistulous anus with a very long spur, and the fourth, by making the disconnection in the upper right part of the abdomen at either the proximal part of the transverse colon or the hepatic flexure

Preparation of the excluded distal colon The contents of the distal colon are washed out, if possible, from the abdominal fistula. It may also be found necessary to wash out the rectum from below the growth. Lavage with antiseptic solution helps to diminish the bacterial content. The longer the distal colon has been defunctioned, the lower the bacterial content is found to be and the better the local condition. In benign conditions, such as a diverticular tumor or the complications arising from it, operation may be delayed for 12 months. In malignant conditions the bowel cannot be defunctioned for more than a month.

Closure of the disconnecting anus. The closure of the small disconnecting anus is very simple. A very long enterotome with a narrow, almost cutting, generously bevelled edge is used. Its length makes a very deep opening in the long spur. A connection can be made between the proximal and the distal segment in a few days (Fig 16)

Types of operation In the defunctioned distal colon, which is quiescent, retracted, and clean, it is possible safely to perform an orthodox sutured anastomosis; and it is still possible to do so even when the segments of bowel to be anastomosed are incompletely peritonealized, or when the disparity in their caliber is great. The use of a sutured anastomosis in the case of carcinoma of the upper and lower parts of the sigmoid is of great advantage, for the requisite amount of bowel which should be removed with the carcinoma and the proper amount of pertaining mesenteric leaf can be critically estimated and then removed, an advantage which does not obtain in operations on the principles of Paul, Mikulicz, and others. In growths in the lower third of the sigmoid this method of operating on the defunctioned colon is valuable. In this situation, any operative methods based on the principle of Paul cannot be satisfactorily carried out because they do not permit an adequate resection of the mesenteric leaf and they do not allow sufficient removal of the bowel on the rectal side of the growth. When, however, the operation is carried out on a defunctioned bowel, the proper amount of the sigmoid and upper part of the rectum with the corresponding part of the mesenteric leaf can be resected, and, with every prospect of success and very little danger, the sigmoid can be anastomosed to the divided rectum. When the repair of this rectosigmoid anastomosis takes place in a defunc-

tioned colon, the incomplete peritonealization of the rectum does not mar the eventual successful healing of the anastomosis.

In some cases of rectosigmoid resection, a sutured anastomosis between the sigmoid and the stump of the rectum

connected and drawn through an opening which is made in this rectal pouch, the sphincter of which is divided. As the sigmoid is functionless and the rectum patulous from the division of the sphincter ani, there is no more danger from this "telescopic" operation than from



Fig 17—Shows diagrammatically the cut end of the sigmoid telescoped into the rectal pouch. A few sutures connect the peritoneum of the sigmoid to the peritoneum covering the rectal pouch, so that as the sigmoid is drawn down, peritoneal surface becomes applied to peritoneal surface. *A*, indicates ring of skin around an artificial anus sutured to rubber tube. *B*, slotted tube fixed in position with a safety pin, used to keep the anastomosis in position and to drain the rectal pouch. *C*, gauze and safety pin which prevent the tube from going up. (Surgery 3 165 1938)

cannot be made because of mechanical disabilities. This happens in fat people, in males with narrow pelvises, and in patients with a small or short rectal stump. In circumstances such as these the rectal stump may be closed, the peritoneum sutured over it and the divided end of the sigmoid implanted into the abdominal wall. Then at a later stage, when the peritoneum has become "glued" onto the rectum, the sigmoid may be dis-

drawing the sigmoid on to the surface of the abdominal wall to make an ordinary abdominal artificial anus (Fig 17).

The method is applicable particularly in serious cases of carcinoma of the lower end of the sigmoid. The telescopic anastomosis can be delayed for from 6 to 12 months, when the patient will have greatly improved in health as a result of the removal of the malignant growth and when the circulation of the

rectal stump, which is sometimes disturbed in these cases, will have improved.

DUODENUM

Duodenal Diaphragm

Intrinsic malformations of the duodenum due to diaphragmatic lesions are discussed by E. G. Krieg.²⁹ Twenty cases have been reported in the literature, to which 1 is added.

A clinical differentiation between duodenal diaphragm and areas of stenosis

cases. The *treatment* is **surgical**. **Duodenojejunoscopy** is preferable to gastrojejunostomy. Nonabsorbable sutures are advisable.

The lesion cannot be detected without opening the lumen of the gut. The only clue to its presence is a dilated proximal segment.

Megaduodenum

Considerable uncertainty still surrounds the conditions of megaduodenum. The term itself merely implies an enlargement, an increased capacity of the

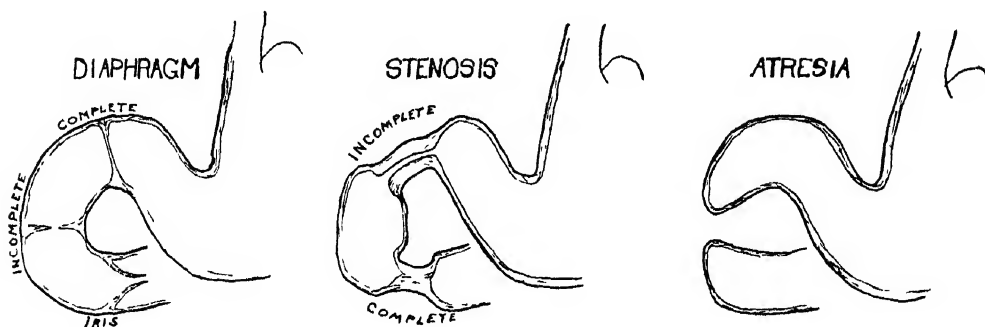


Fig. 18—Drawings illustrating Forssner's classification of intrinsic duodenal malformations (Ann Surg 106 33, 1937)

and atresia cannot be made in the first weeks of life because the clinical pictures may be identical. Later a more definite diagnosis can be made. At all ages, x-ray studies and the clinical findings. In the correction of these lesions, certain technical considerations improve the result obtained.

Diaphragmatic obstructions may be encountered throughout life. The earliest age reported was that of a still-born infant, and the oldest 70. In contrast, the patients with stenosis rarely live more than 4 weeks. Clinically, the symptoms of the condition are those of pyloric obstruction, and they may be acute or chronic. Pain in the upper quadrant is present in most cases. Constipation is present in varying degree. Visible peristalsis is present in 25 per cent of the

duodenum, without reference to the causes of the condition. J. Nordentoft³⁰ points out that these causes may be extrinsic or intrinsic. Without doubt any disorders or abnormalities in any of the many widely different organs closely surrounding the duodenum may affect the anatomy and physiology of that organ itself. Besides this, abnormalities in the duodenum itself, congenital or acquired, may cause pathological dilatation of the organ. The most frequent and best known cause of megaduodenum is duodenal stenosis, either congenital or of later development on a pathological basis.

Two cases of megaduodenum are reported by the author from observations made by him at the State Hospital in Copenhagen. The first of these was one

of true duodenal stenosis due to congenital organic malformation. The patient, a girl of 2 years, was admitted to the hospital with a history of copious, intense vomiting since birth. Usually the vomiting would occur a long time after a meal. For instance, carrots would be ejected about 5 days after ingestion. Almost any food given her would be ejected, even oatmeal soup. Naturally she was thin and of slender build. Roentgenological examination showed the duodenum to be much enlarged with stenosis at the junction of the duodenum and the jejunum. Operative findings disclosed an enormous duodenum with thick, gray, hypertrophic walls. The circumference of the duodenum was about the same as that of the stomach. The pathogenetic conditions could not be determined with certainty. Duodenojejunostomy was performed with salutary results. The operation failed to reveal any stricture, though both the previous history and the clinical picture suggested it. Moreover, the roentgenological examination had shown a canalicular constriction at the junction of the duodenum and the jejunum.

The second case reported by the author was one of megaduodenum in which no positive cause for the existence of the condition could be demonstrated. Clinically the picture was very different from that of the first case. The patient, a young man of 25 years, had been suffering from periodical pressure pains in the epigastrium since childhood, but never with vomiting. Roentgenological examination showed a greatly dilated duodenum, simulating the stomach in size. In this instance no stenosis could be detected. Operative findings disclosed a strongly distended duodenum embedded in a close network of adhesions. Nothing could be demonstrated, however, which would reasonably explain the

cause of the condition. Stenosis could not be demonstrated, while the numerous adhesions between the duodenum and the surrounding tissues could be regarded as secondary changes. The duodenojejunostomy gave excellent results. This was, certainly, a case of megaduodenum of doubtful origin.

The author points out that in all probability all transitions may be found, from very slight enlargement to extreme dilatation, with a surprising absence of symptoms. With so much uncertainty still surrounding the condition of megaduodenum, it becomes imperative that all cases be studied with great care. The roentgenological diagnosis, with observations especially as to motility, is of great value; stenosis can sometimes be demonstrated by it; whereas experience has shown that it is frequently difficult, or even impossible, to discover the cause of megaduodenum by operation. The condition of the stomach also should be observed with a view to the possible detection of any disorder which might possibly affect the nerve supply of the duodenum.

Duodenitis

Duodenitis must be differentiated from duodenal ulcer, gall-bladder disease, pancreatitis, appendicitis, and colitis. In 1934 Kirklin described an x-ray examination which may show pathognomonic findings.

The series of cases reported by G Garry³¹ comprised 20 of simple duodenitis, verified by operation and by microscopic examination of excised tissues. The diagnosis was not made preoperatively in any of the cases. Thirteen were diagnosed erroneously as duodenal ulcer, and the remainder as gall-bladder disease, appendicitis, and colitis.

Treatment—In discussing the surgical treatment, emphasis should be placed

upon the fact that duodenitis is essentially a medical condition and surgery is utilized only in those cases in which medical measures have been of no avail. The author's experience with gastroenterostomy has been unsatisfactory. This operation was done in 13 cases with good results in only 3. Five are described in detail.

In the discussion, emphasis is placed upon the similarity of microscopic findings in duodenitis to those found in appendicitis. "In both conditions the mucosa is only lightly affected while the intensity of the process is confined largely to the muscular coats." The intensity of the process is largely confined to the muscular coats and varies from a very moderate degree to a very intense degree in which there is almost a phlegmonous inflammation of the duodenal muscularis.

The cases reported show the disproportion between the symptoms and the anatomical findings. The severest clinical manifestations are often found in conjunction with insignificant operative findings. Under these circumstances the surgeon finds himself in a predicament about the correct diagnosis and the proper procedure to follow. It is important, therefore, to establish as far as possible an accurate diagnosis preoperatively. Once the diagnosis of duodenitis is established, the only recourse left for obstinate cases refusing all internal therapy is operation. It appears to the author that gastroduodenal resection should be the method of choice.

The Problem of Duodenal Ulcer

The literature concerning duodenal ulcer is so voluminous each year and so many of its aspects are controversial that a review and evaluation of the problem occasionally seems indicated.

O. T. Clagett, K. R. Trueman and W. Walters³² state that most writers now agree that the term "peptic ulcer" should be discarded and that in any discussion very careful distinction should be drawn between the terms "duodenal" and "gastric" ulcer. These 2 lesions are dissimilar biologically, physiologically, and pathologically. For example, Walton has stated that approximately 10 per cent of gastric ulcers become cancerous and that approximately 20 per cent of cancers of the stomach originate from gastric ulcers, whereas a primary duodenal ulcer rarely if ever undergoes malignant change. From the standpoint of treatment an essential difference also exists. In resection for gastric ulcer relative achlorhydria almost invariably follows the Polya and Billroth I procedures and recurrence practically never takes place. On the other hand, Klem, Aschner and Crohn have reported that relative achlorhydria results in from only 60 to 70 per cent of the cases following the Polya operation, and Walters and Wolff in approximately 25 per cent following the Billroth I resection for duodenal ulcer. Graham has said, "much harm, confusion, and disastrous therapy" come from considering these 2 conditions as a single entity.

Medical treatment has become established on a firmer basis and, with greater experience and better diagnostic tests, it has been possible to determine more accurately which patients will respond best to medical treatment. The surgical indications for the treatment of duodenal ulcer are also better appreciated and there is a definite tendency to suit the surgical procedure to the individual patient. The indications for partial gastrectomy for duodenal ulcer are also becoming clearer. There has likewise been much controversy concerning the subject of bleeding duodenal ulcer, but from

these numerous, almost diametrically opposed opinions there has developed sounder judgment of the indications for, and the value of, the various types of treatment.

Gage and his associates have pointed out that the most important factors in the causation and persistence of peptic ulcer are: (1) The inherent constitutional predisposition to form ulcer, that is, the ulcer diathesis; (2) the tissue susceptibility to ulcer, and (3) the increased gastric acidity because there is probably little that can be done to change the inherent predisposition and the susceptibility of the tissues. This attitude is definitely sound, and just as gastric acidity must be controlled to heal an ulcer, it must continue to be controlled to prevent recurrence after healing by any form of treatment, medical or surgical. That certain individuals from certain localities have a greater predisposition to peptic ulcer or a greater tissue susceptibility to ulceration is true beyond a doubt. It is unfortunate that we have no definite method of measuring this predisposition in tissue susceptibility. Such a method would be of inestimable value in determining the therapeutic procedure to be carried out in a given case. Without such a method one must depend on a careful clinical study and analysis of the case, considering the gastric acid values and the roentgenological and gastroscopic reports

In summarizing, the problem of treatment of duodenal ulcer is still unsolved. No methods of treatment have been advanced that uniformly control gastric acidity in every case. Statistics seem to be of small avail in consideration of the individual case, and each patient must be treated according to the merits of his individual case and all the factors relating to it. Recurrence of ulceration in every case means that: (1) Gastric acid-

ity has not been adequately controlled; or (2) the patient is constitutionally predisposed to peptic ulcer and has a marked tissue susceptibility to ulceration. Tissue resistance to inflammation and ulceration from the hydrochloric acid of gastric secretion is what the successful surgical treatment of duodenal ulcer depends on, for if the tissue is resistant to hydrochloric acid, the patient will have a good result from the recognized types of surgical procedures without recurring ulceration; whereas if the tissue is susceptible to ulceration and if hydrochloric acid continues to come in contact with such susceptible tissues, ulceration will recur. Unfortunately there is no way at present to measure tissue resistance to acid gastric secretion.

Acute Massive Hemorrhage from the Upper Gastrointestinal Tract

Few conditions create more uncertainty and alarm than the rapid loss of large quantities of blood from the gastrointestinal tract. The patient with little or no nausea may suddenly vomit a basinful of blood, or upon a sudden desire to defecate may yield a large liquid stool tarry black or even showing bright red blood. He may exhibit varying degrees of shock with pallor, sweating, restlessness, and rapid pulse.

In a previous study of 371 bleeding duodenal ulcers occurring over a 10-year period at the Massachusetts General Hospital A. W. Allen³³ found that 22.6 per cent of the patients had hematemesis only, 38.3 per cent had melena only, and 39.1 per cent had both hematemesis and melena. While the most frequent source of such massive hemorrhage from the upper gastrointestinal tract is the duodenal ulcer, there are several other types of lesions which produce the same picture. These are gastric ulcer, gastric carcinoma, gastrojejunal ulcer, esopha-

geal varices, leiomyosarcoma, and hypertrophic gastritis.

During a 10-year period, the diagnosis of duodenal ulcer was made in 1002 ward patients. Of this number, 390 had gross bleeding while under observation. Ninety-four bled profusely, in sufficient amounts to produce shock and acute anemia. Forty-eight were classed as severe bleeders. All these patients were found to have a red blood count below 3,000,000 and hemoglobin below 70 per cent. Thirteen of these patients bled to death. In an analysis of the cause of fatal bleeding, the writer found that the age of the patient was a most important factor. Thus in 90 patients who were under 50 years of age and who bled profusely, only 4 died. Among 42 patients over 50 years of age, 14, or exactly one-third, died of hemorrhage. Further, it was found that if operation was delayed for a week or more in a patient continuing to bleed either constantly or repeatedly every day or 2, he was not saved by surgery regardless of what was done. Nine of 20 patients with massive hemorrhage died during their first period of bleeding.

In the early hours of acute massive hemorrhage from duodenal ulcer if the patients are under 50 years of age with elastic blood vessels, conservative measures are indicated, because it is unlikely that they can be operated upon and the vessels be ligated with a mortality of less than 5 per cent. In the older age group, we can use Finsterer's much quoted 48-hour time limit to advantage.

The deep penetration of the posterior wall ulcer into pancreatic tissue, at a point where the gastroduodenal artery traverses it, increases not only the risk of continued bleeding but makes any operative procedure one of major consideration. One can hardly expect to open the anterior wall of the duodenum

and successfully place ligatures in this friable ulcer bed, nor can one pass stitch ligatures in this friable ulcer bed, nor ligatures in such a way as to occlude the vessels in healthy tissue from within. This method has succeeded only in isolated instances. Finsterer advocates direct tamponade in some extensive ulcerations into the pancreas with a later secondary resection after recovery from acute blood loss and shock. In a large group of patients with active bleeding ulcer, he has successfully ligated the bleeding vessels and resected the distal two-thirds of the stomach with a low 5 per cent mortality, if the operation was undertaken within 48 hours after the onset of bleeding. In the patients with ulcers bleeding 1 week or more, the mortality has been 30 per cent. Finsterer apparently believes that by excluding the extensive, deeply penetrating ulcer on the posterior wall of the duodenum, by transection of the duodenum proximal to the ulcer, or by transection of the antrum 2 fingerbreadths from the pylorus, and then by removing the distal two-thirds of the remaining stomach, his end results are nearly as good as when the ulcer in the duodenum is included in the resection. Finsterer calls this operation "resection for exclusion." The author is of the opinion that in doing this operation the radicles leading into the ulcer bed are ligated. Many surgeons have found gastroenterostomy a failure for the treatment of massive hemorrhage in duodenal ulcer.

In the quiescent or interval stage of duodenal ulcer of the posterior wall, especially after one or more episodes of massive bleeding, one is confronted with the problem of proper treatment. If the patient is young and responds well to a dietary regimen, we may justly consider that radical surgery is meddling. Certainly some of these patients manage to

get along comfortably and safely for many years. In those individuals with recurrences of massive hemorrhages, it is believed that radical surgery makes possible a safer and more comfortable life. In 38 consecutive cases of duodenal ulcer of the posterior wall, the author resected the distal one-third or two-thirds of the stomach and when possible the ulcer-bearing portion of the duodenum, and followed this with a posterior Polya anastomosis. All of the 38 patients had bled severely, but all recovered from the operation and remained well for varying periods of time. Some of them developed new ulcers either at the stoma or on the lesser curvature of the remaining portion of the stomach. In each case of newly formed ulcer, there have been episodes of hemorrhage. None of these patients have thus far died from hemorrhage. They were undoubtedly protected from fatal bleeding by the ligation of the large vessels overlying the head of the pancreas. However, their ulcer diathesis and their hemorrhagic tendency as well have not been altered. The author is now trying a more radical resection of the stomach.

Details as to the conservative management of massive hemorrhage have not been considered a part of this discussion. However, certain aspects demand consideration. *The author has never seen a patient die as a direct result of a blood transfusion, but we have all seen patients die from the lack of a transfusion.* Everyone is in accord with regard to the importance of blood replacement. Sedation of the actively bleeding patient has been a questionable procedure. Finsterer warns against too much morphine in these depleted patients prior to operation; however, the restless stage of shock may be decidedly harmful, and doubtless there is a proper middle course. An in-lying Levine tube may be worthy of

consideration. The tube allows aspiration of gastric and salivary secretion, which may hinder clot formation. It serves to identify fresh episodes of bleeding. Without doubt, it serves to minimize peristaltic activity and eliminates vomiting, which in itself may dislodge a lifesaving thrombus in an open vessel. The entire basis of treatment consists of perfect rest, quiet, and comfort.

Primary Tumors of the Duodenojejunal Tract

Lymphogranuloma of the Duodenum—Among the various malignant tumors of the gastrointestinal tract, those of the duodenum are exceedingly rare. In a series of 500,000 autopsies an incidence of only 0.3 per cent has been reported. According to M. Cace,^{3,4} malignant neoplasms of the jejunum, however, are less rare, their incidence being about 1 per cent. It is not surprising that the diagnosis of malignancy of the duodenum is exceedingly difficult in the live patient.

The first roentgenological reports of these lesions were incomplete and inadequate. The author had the opportunity in 1933 and 1934 to observe 6 patients presenting malignant lesions of the upper intestinal tract. These lesions were all localized below the insertion of the Mesocolon and above the ileum, 4 of the tumors were localized at the second portion of the duodenum, 1 was localized at the papilla of Vater, and 1 was found to involve the first loops of the jejunum. Five of the tumors were carcinomas and the sixth represented an inflammatory hyperplastic process of probably lymphogranulomatous character.

On the basis of clinical and roentgenological studies of these cases, Cace concludes that primary malignant tumors of the duodenum may cause a more or less extensive stenosis. The mucosal outline is lost, the elasticity is decreased, and

peristalsis is abolished. The stenosis is accompanied by a tumefaction of this portion of the intestine which in turn gives rise to pressure effects upon the duodenum and the antral portion of the stomach, without causing, however, alterations of the pyloric outline and the duodenal cap. Important diagnostic signs in this respect are the absence of perivisceritis of the adjacent organs, and a well-delimited area of stenosis with the re-appearance of the mucosal outline just beyond that portion of the duodenum which has not been invaded by the neoplastic process.

The aforementioned stenosis may be accompanied by the appearance of more or less extensive filling defects and in this case the intestinal wall presented an irregular or circinate contour. In some cases there may be roentgenological evidence of small or large ulcers presenting ragged borders. Duodenobiliary fistulas have also been visualized in these conditions.

According to the author, tumors originating at the papilla of Vater are characterized by their "flame-like" appearance. This finding is of greatest importance in the diagnosis of a malignancy involving the papilla of Vater.

Cancer of the Duodenum—A clinical and roentgenographic study of 18 cases of primary carcinoma of the duodenum collected from the material of New York Hospitals was made by W. J. Hoffman and G. T. Pack.³⁵ In 5 of the cases the patient was studied during life by the authors. All were instances of true carcinoma of the duodenal mucosa. Cases of carcinoma of the ampulla or of the papilla of Vater are not included.

Incidence—The rarity of primary carcinoma is indicated by its incidence of 0.033 per cent in 350,286 autopsies.

The sex incidence shows a preponderance of males of 3 to 1.

The usual pathological type is some form of adenocarcinoma arising from the duodenal mucosa. The gross forms may be scirrhous, bulky and polypoid, or colloid. The pathological findings in these 18 cases are summarized.

Symptoms—The symptoms of duodenal carcinoma are chiefly those due to obstruction of the duodenum and neighboring structures. The early stages are featured by anorexia, gaseous eructations, epigastric distention, and nausea. As obstruction develops, these become more severe, and pain, vomiting, dehydration, loss of weight, and constipation quickly follow. A palpable tumor is found in more than half the cases. The sloughing away of portions of the tumor may temporarily relieve the obstruction or give rise to severe hemorrhage. When the bile passages are obstructed, jaundice of a constant, unrelenting type develops. The progress of the disease is swift, and the loss of weight may be extreme.

The average duration of life is about 7 months after the onset of symptoms. The shortest duration of life is found in cases in which the lesion is around the ampulla, the longest duration, in those in which the lesion is in the first portion of the duodenum.

In almost every case of duodenal carcinoma which is studied roentgenographically definite pathological changes can be demonstrated. Such evidence was present on the films in 15 cases in which such studies were made. In 14 of these the pathological process was recognized and described. In only 1 instance, however, was the possibility of a primary carcinoma of the duodenum suggested.

Treatment—The treatment of primary carcinoma of the duodenum is pre-eminently surgical. The operative mortality is high. It amounted to 58.3 per

cent in the authors' series of cases. In a large percentage of cases at operation there is no evidence of metastasis or local extension of the disease. The surgical removal of all of the malignant tissue might therefore often be feasible if this mortality could be brought down to a reasonable level by efforts to combat the effects of the intestinal and biliary obstruction prior to operation. The patients show advanced degrees of starvation, dehydration, alkalosis, anemia, jaundice, and gastric distention. Measures recommended in the preparation of the patient for operation are the restoration of body fluids, mineral salts, carbohydrates, and blood supply. Various surgical procedures which have been employed are described, discussed, and illustrated

GALL-BLADDER

Chemical Composition of Bile—

The chemical composition of the bile of the liver and of the normal and pathologic bile of the gall-bladder has been investigated by E. Prado Tagle and G. Kurth³⁶ On the basis of their observations they reach the conclusion that impairment of the gall-bladder is characterized by an almost 100 per cent increase in the mucin content of the bile. There is also a considerable increase in bile salts. The dry residue is low, which indicates a decrease in the substances that are dissolved in bile and thus also a reduction in the concentration capacity of the gall-bladder. The bilirubin and cholesterol contents are normal.

These observations suggest that, in case of impairment of the gall-bladder, that chemical function of the liver which concerns the formation of bile acids is impaired. It seems to be reduced. In contradistinction to this, the capacity for the elimination of cholesterol and bili-

rubin is intact. The content of these "waste substances" frequently is even increased. This disturbance in the chemical function of the liver is probably a contributing factor in the development of gallstones for bile salts facilitate the solubility of cholesterol and bilirubin. The lack of these substances favors the precipitation of the lipoids and of the biliary pigments. These factors throw light on the pathogenesis of gallstones, particularly if the increase in mucin is likewise taken into account. The latter interferes with the evacuation of the gall-bladder, because it increases the viscosity. This in turn produces biliary stasis and favors the growth of microbes in the infected gall-bladder. Mucin promotes the accumulation of sediments. This is important for the formation of the nucleus of gallstones. The supersaturation phenomena of cholesterol and bilirubin promote the growth of gallstones around this nucleus.

Chemical Factors in the Formation of Gallstones—

According to R. E. Dolkart and his associates³⁷ in all the various bile salt preparations used in the experiments the sodium salt of pure cholic acid proved to have the greatest cholesterol-solvent capacity, with sodium taurocholate, sodium desoxycholate and sodium glycocholate in the order named, next in activity. There appears to be an optimal concentration for some of the preparations used. Changes in the structure of the bile acid molecule have a marked effect on the ability of the particular acid to hold cholesterol in solution. Conjugation with aminoacetic acid or taurine somewhat decreases this ability. The oxidation of desoxycholic acid to the keto form resulted in a marked loss of solvent capacity. Mixed ketocholanic acid showed moderate ability to hold cholesterol in solution, and it appears that some additional substance—

possibly chenodesoxycholic or lithocholic acid—is present. The authors' results demonstrate that bile salts are not the most essential substances for maintaining cholesterol in solution in the bile. In equivalent concentrations the fatty acids were far more active as cholesterol solvents than were the bile acids. The studies of the cholesterol—solvent capacity of fractions of bile showed that whether or not the animal belonged to a species which forms gallstones, if the bile was solvent for cholesterol, the solvent capacity could be isolated in the saponifiable or fatty acid fraction. There was a considerable decrease in the amount of this saponifiable fraction in relation to the cholesterol content of the bile in those animals which form gallstones, as compared with the amount in those which never form gallstones. Whether the fatty acids as they occur in the bile function independently in maintaining the nonsaponifiable material in solution in the bile or whether they act in combination with the bile acids, as suggested by Wieland and Sorge and Verzar, cannot at present be determined. However, more attention should be given the rôle of the fatty acids in the production of gallstones.

E. Chabrol, J. Cottet and M. Cachin³⁸ review the literature on the rôle of the biliary salts, the fatty acids and cholesterol in the development of biliary lithiasis and report their own investigations on this problem. In studying *in vivo* the relations between cholesterol and cholic acid they direct attention to the inconstancy of hypercholesterolemia in patients with biliary lithiasis. They show that there is no excess of cholesterol in the gall-bladder of patients with lithiasis and that there is no balance in the hepatic excretion of cholesterol and of cholic acid. They report *in vitro* studies on the relations between cholesterol and cho-

lalic acid and demonstrate that the cholesterololytic power of the bile of dogs is not strictly dependent on its initial cholesterol content or on the cholic acid content. They report studies on the relation of cholesterol and of cholic acid to the biliary hydrogen ion concentration and then inquire whether the elective absorption of the biliary salts by the vesicular wall leads to the formation of calculi of cholesterol. They point out that it would be exaggerated to reduce the pathogenic problem of lithiasis to a balance of cholesterol and of cholic acid, in other words, to a selective insufficiency of the biliary salts. The deficit of the fatty acids also plays its part by disturbing the unstable emulsion of colloids and crystalloids. On the other hand, the amount of secreted albumin and the variations in the pH caused by the acidifying microbes may precipitate the cholesterol without necessarily acting on the cholic acid. Whether stasis of the gall-bladder, which facilitates infection, or hepatopancreatic insufficiency with its disturbing influence on the metabolism of fats, pigments and biliary salts is incriminated, in all the hypotheses the problem of lithiasis is dominated by the notion of colloidal disequilibrium. Closely united in their destiny, cholesterol and cholic acid seem to undergo this disturbance more often than they cause it by their excess or by their deficit.

Alterations of the Contractile Portion of the Gall-Bladder Wall in Various Forms of Gall-Bladder Disease—Twenty-four gall-bladders presenting various forms of gall-bladder disease have been examined by G. Baz-zocchi³⁹ and after discussing in detail the normal histological features of the gall-bladder, he studied the pathological alterations encountered in cholecystitis, cholelithiasis, and lipoidosis.

He found that the fundamental features of lipoidosis consist of hypertrophy and hyperplasia of the mucosal and muscular layers, whereas in cholecystitis and cholelithiasis he encountered a marked sclerosis of the gall-bladder wall.

In cases of gall-bladder lipoidosis, phenomena of dysfunction and dyskinesia predominate, whereas in cases of cholecystitis and cholelithiasis, inflammatory phenomena are apt to appear. Any combination of these 2 fundamental lesions may be encountered in the various forms of gall-bladder disease.

Bazzocchi believes that hypertrophy and hyperplasia of the epithelial portion of the gall-bladder wall must be considered as morphological expressions of its dysfunction. The sclerosis, on the other hand, cause an abolition of mobility and function of the gall-bladder.

The reticular framework of the mucous membrane follows the same fate as that layer, and becomes hyperplastic and hypertrophied in conditions of lipoidosis, whereas it undergoes a scleroreticular or collagenic metaplasia in inflammatory or necrotic conditions. The histopathological aspects of the elastic portion of the mucous membrane vary in the various forms of gall-bladder disease.

The muscular layer undergoes the same changes as the mucous membrane and becomes hypertrophic in lipoidosis and atrophic or fibrotic in inflammatory conditions. The argyrophil reticulum of the muscular layer is divided into an interstitial and perimuscular portion. The interstitial layer follows largely the fate of the collagenic fibers, whereas the perimuscular layer follows the fate of the smooth-muscle cells. The elastic network is thickened if the collagenic fibers begin to show proliferative changes.

The subserosal layer presents features which are different from those encount-

ered in the mucosa. It is soft, and in gall-bladders with a marked mucosal hyperplasia, its volume is decreased. In gall-bladders presenting a sclerosis and atrophy of the mucosa, on the other hand, the subserosal layer is thickened and infiltrated. The reticular network, which normally is very scarce, forms argentaffine aggregations in all places where infiltrates are present. The elastic fibers, which are normally quite abundant in the external layers, increase in number, especially in cases presenting a sclerosis or a pericholecystitis.

In general, it may be stated that the contractile portion of the gall-bladder is always altered in these conditions, but the changes depend upon the individual type of gall-bladder disease.

The author points out that in the contractile mechanism of the gall-bladder the smooth-muscle cells are of prime importance. Contrary to common belief, in all forms of the cholecystitis without jaundice, the "colic" is not due to the possible presence of a stone, nor to a hyperkinesia, because of the fact that the contractile elements are almost completely destroyed. Also, the severe pain is not due to hyperdistension of the gall-bladder because the rigidity of its wall is considerably increased.

Gall-bladder Disease

Etiology — A clinical and experimental review of the literature on the influence of pregnancy and the genital function on gall-bladder disease is followed by an exhaustive clinicostatistical report on 1000 cases of cholecystitis collected at the Surgical Clinic of Bologna from 1921 to 1937 by G. Bendandi.⁴⁰ Of the 1000 patients 67.4 per cent had stones and 32.6 per cent had a lithiasis; 90.5 per cent were females and 9.5 per cent were males. Eighty-five and nine-tenths per cent of the 905 fe-

males had had 1 or more pregnancies, while 12.9 per cent were nulliparous. Of the 610 women with stones in the gall bladder 8.03 per cent had never been pregnant, whereas 90.49 per cent had had deliveries 1 or more times. In approximately 20 per cent of the cases the first clinical symptoms of the disease occurred during pregnancy, the puerperium, or soon afterward. The author believes that the data of this statistical study confirms the evidence in the literature that there is a certain influence of gestation on gall-bladder disease, especially gall-bladder infections with stones.

That pancreatic juice may be a factor in the etiology of gall-bladder disease is shown by J. A. Wolfer.⁴¹ Under normal conditions the bile passes through the ducts to be emptied into the duodenum, some entering the gall bladder to be concentrated and later to be expelled into the common duct. The pancreatic juice may enter the duodenum by a direct passage or may fuse with the bile in the ampulla. With low grade stasis in the biliary passages such as may be produced by distended papillary function or by complete or incomplete obstruction at the duodenal end of the biliary and pancreatic ducts, the bile mixed with pancreatic juice may remain in the ducts for a considerable time, the bile-pancreatic juice ratio being altered, and variable amounts of pancreatic juice enter the gall-bladder.

The disturbance created in the gall bladder will then depend upon known and unknown factors. If the pancreatic juice content is low and no bacterial contamination is present, no changes may occur in the wall of the gall bladder. If, however, the pancreatic juice content is higher, the stasis prolonged, and possibly a low grade bacterial contamination is present, changes may occur as described by Andrews, Goff, and Hrdina.

They have shown with the introduction of pancreatic juice into the gall bladder of the dog that the cholesterol content of the bile is not altered, but that the concentration of the bile salts is reduced to less than one-third. In 5 experiments, with unfiltered pancreatic juice, all the bile salts had been absorbed leaving the cholesterol precipitated. Therefore, in the human being, the low dilution stage may be a factor in the production of gallstones. When the concentration of pancreatic enzymes in the gall-bladder bile is high, the pathologic changes produced will depend upon complete or incomplete activation of the pancreatic enzymes in greater or lesser dilution in contact for short or long periods of time, sufficient time and concentration being necessary for necrosis.

It is not the purpose of this paper to convey the idea that all cases of cholecystitis or gallstones are produced by a reflux of pancreatic juice into the gall bladder; however, the author is convinced that the cause of selected cases of acute necrosis and acute gangrenous cholecystitis and also cases of chronic cholecystitis with or without stone can be found in a reflux of pancreatic juice into the gall bladder.

In *children* there can be little doubt that infectious disease of some part of the digestive tract is one of the principal causes of gall-bladder disease in children. A. H. Potter⁴² points out that typhoid fever has been mainly incriminated. Since the incidence of typhoid in the United States has greatly diminished with no relative change in the incidence of gall-bladder disease, one must look for other contributory factors such as infections of the upper respiratory tract, including influenza and pneumonia, scarlet fever, appendicitis, intestinal parasites, and sometimes a history of abdominal trauma.

TABLE II
BUREAU OF CENSUS REPORT* ON ETIOLOGY, AGE, SEX, RACE

A—Deaths in children under 15 years of age from causes considered etiological factors in biliary tract disease, in white, Negro, and other races.

	Males	Females	Total
Infectious and Parasitic Diseases	13,201	12,807	26,008
Appendicitis.....	1,767	1,427	3,194
Influenza, Respiratory Complications Specified	1,277	997	2,274
Scarlet Fever	949	843	1,792
Typhoid Fever.....	248	280	528

B—Deaths from biliary calculi in children not over 15 years of age, including males and females, white and others, none.

C—Deaths from other diseases of gall-bladder and biliary passages in children not over 15 years of age.

	Under 1 Yr	1 Yr	2 Yrs	3 Yrs	4 Yrs	5 to 9 Yrs.	10 to 14 Yrs.	Total
Males—								
White	4	0	4	2	2	4	2	18
Negro	0	1	0	0	1	1	1	4
Other Races	0	0	0	0	0	0	0	0 22
Females—								
White	1	3	0	2	1	1	4	12
Negro	1	0	0	0	0	0	1	2
Other Races	0	0	0	0	0	0	0	0 14

(Surg, Gynec and Obst 66 604-610 (Mar) 1938)

* The Bureau of Census report on deaths by age, sex, and color or race in the Registration States (including District of Columbia), 1920 to 1934. (*Vital Statistics—Special Reports* 1 86, 1936)

Cholecystitis may also be a complication of the systemic infections of childhood. A moderately large number of cases have been observed in the convalescent stage of scarlatina. Schottmueller details 5. Saxl and Gross and Ssawrimowitsch report similar instances. Schottmueller associates hepatitis with the cholecystitis in his cases, and believes that the toxin of the hemolytic streptococcus and not the microbe itself affects the liver and gives rise to the complication.

The possibility of a congenital origin of biliary tract disease, as illustrated in the cases of Melchior, of Brooks, and of Dotti, must not be overlooked.

Zelditch, *et al.*, in some of the cases observed by them, associated cholecystitis with lamblasis, the latter being the etiological factor of the former.

Diagnosis—Cholecystography—L. J. Rigney and his associates⁴³ made a diagnosis of cholecystitis, with or without stone, in the cases of 30 per cent of their patients who complained of digestive symptoms. Observations of a group of operatively proved cases indicated that duodenal drainage and cholecystography, together, rarely failed to be of aid in the diagnosis of gall-bladder disease.

In each of the authors' 137 cases, 1 or more satisfactory duodenal investigations and at least 1, often 3 or 4.

reliable cholecystographic investigation was made previous to operation. When the question of function arose, the authors were inclined to record it as good, rather than as poor or impaired.

Operations for the removal of the gall-bladder were performed in the cases of 120 patients, following which a microscopic and gross examination of the organ was made. The cases were unselected except for the elimination of those which, in a preliminary study, had been found unsatisfactory.

The cases are considered in 2 main groups, patients with stones (100), and patients without stones but with evidence of some gall-bladder pathology (37). Each group is discussed separately. A third group of 12 cases, made up of certain cases from the 2 main groups and composed of patients having gall-bladders of the "strawberry" type, is also discussed. Included in the article are tables showing the age, sex incidence, diagnostic significance of various observations, and conflicting observations in the consideration of these cases by means of cholecystography, duodenal drainage, and operation.

In the diagnosis of gall-bladder disease, the authors believe that: (1) The history and physical signs are of great importance and may occasionally justify operative therapy even in the presence of negative roentgenological and biliary tests; (2) a positive diagnosis of stone in the gall bladder can be made on the basis of negative shadows in cholecystography, or, in not more than half of the cases, by the presence of cholesterol crystals in biliary drainage material; (3) by means of either of these tests a diagnosis of gall-bladder disease can be made in approximately 90 per cent of the cases with stone and in 50 or 60 per cent of those without stone, but that a strict diagnostic classification on the basis of

the presence or absence of stone is frequently impossible, and (4) both tests should be employed routinely in cases of suspected gall-bladder disease, as a check on information obtained from the history and physical examination of the patient. In some instances, cholecystography, and in other instances duodenal drainage, will give important diagnostic aid. Together, they failed to be of help in only 3 of the authors' cases.

A more *physiologic technic* in *cholecystography* is outlined by R. Impalomeni,⁴⁴ who points out the importance of stimulating bile secretion in visualizing the gall-bladder. He followed the behavior of cholecystography as it was done by Graham's technic or after administration of an intravenous injection of a mixture of either bile salts or liver amines and the opaque substance. The mixture was prepared by adding either 10 cc. of a 20 per cent sodium dihydrocholate solution or 3 or 4 cc. of the preparation of liver amines to 30 cc. of the opaque substance. The mixture was prepared by adding either 10 cc. of a 20 per cent sodium dihydrocholate solution or 3 or 4 cc. of the preparation of liver amines to 30 cc. of the opaque substance. The author carried on his work in 2 groups of persons, normal and those with hepatobiliary diseases, the number not being specified. The tests were performed during a fast. The author concluded that when Graham's technic is resorted to the gall bladder of normal persons is visualized in 2 hours as a small clear shadow, the size and darkness of which gradually increase. Distention of the gall-bladder and elimination of bile by the structure early in the course of the test do not take place. The gall-bladder of normal persons is visualized within 15 minutes in the course of the combined cholecystography by bile salts in the opaque substance. By the end of the first

hour, it is entirely visible. By the end of the second hour, it is as clear as after 8 or 10 hours when Graham's technic is used. Bronner's test, after the administration of 2 or 3 egg yolks, empties the gall-bladder in the same manner and length of time as Boyden's meal does during the Graham test. Cholecystography by the combined method of liver amines in the opaque substances give clearer and quicker results than those

stage, *i. e.*, not yet dry and porous and surrounded by mucus, and composed of substances ranging all the way from the pure cholesterin (specific gravity 1.040 to 1.056) to the calcium stone of much higher specific gravity, were introduced into extirpated gall-bladders, wax phantoms of gall-bladders, and into living gall-bladders, and roentgenograms were taken under conditions simulating those of the clinic.

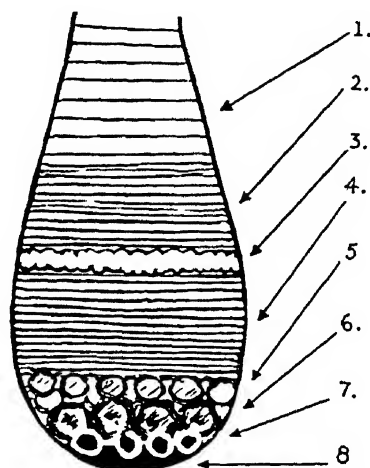


Fig 19—Schematic drawing combining all the different types of stratification and sedimentation in the gall bladder (1) Native bile (bile containing no contrast material), (2) contrast bile (less highly concentrated), (3) suspended gallstones, (4) contrast bile (more highly concentrated), (5) concrements with small calcium content, (6) concrements with high calcium content, (7) completely calcified concrements, (8) amorphous calcium sediment (Acta radiol, 1938)

obtained by Graham's technic but more slowly than those obtained with bile salts.

Progress in the *roentgenological* diagnosis of gallstones as a result of studies on the conditions of sedimentation and stratification in the gall bladder is disclosed by A. Akerlund^{4,5}. He supplements the subject of clinical possibilities with a wealth of new material and experimental evidence which tends to substantiate his theory that biles of differing specific gravities are the cause of the phenomenon of stratification. Fractions of bile, or even of plain water, containing different dilutions of the contrast material (thorotrast) and gallstones in a fresh

From his studies the author concludes that although the heavy bile containing contrast medium and the lighter native biles do not mix completely in the gall-bladder there is no abrupt demarcation, the materials of different specific gravities being suspended at different levels, and he constructs a schema illustrating his findings (Fig 19).

Added clinical material demonstrates the assertion that in every case in which gallstones are suspected the new method will either rule out their presence with greater certainty, or, by the suspension on a line at a uniform level or by a half-moon-shaped sedimentation at the

bottom of the gall bladder, even of small transparent groups of stones, it will at times enable a diagnosis which could not otherwise have been made.

Acute Cholecystitis—In recent years there has been a swing in surgical opinion toward earlier intervention in acute cholecystitis.

Five years ago, in an endeavor to clarify his ideas on the subject, M. K.

amounting to 436 cases over a 17-year period. Of these patients, 356 were operated upon with a mortality of 8.3 per cent. Of the 80 patients who were not operated upon, 6.3 per cent died.

The incidence of empyema, gangrene, and perforation increases as the attacks are prolonged. In the St. Luke's Hospital series, 27 per cent of these conditions developed in the first week, 31 per



Fig 20

Fig 20—Fundus sediment with a half moon-shaped agglomeration of tiny, transparent stones. At the bottom is seen a thin layer of amorphous calcium sediment (incipient "calcareous or limy bile")



Fig 21

Fig 21—So-called fundus-diverticulum or hourglass gall-bladder. Horizontally suspended stratum, consisting of a large number of extremely small cholesterin stones. A few hours previously the suspended layer of stones lay entirely beneath the obliquely directed infolding of the gall-bladder wall (fundus diverticulum). The diagnosis of stone was only possible by means of the sedimentation roentgenogram (Acta radiol., 1938)

Smith⁴⁶ analyzed a series of 201 patients who came to operation for this condition at St. Luke's Hospital, New York. The mortality of the series was 7.3 per cent. Dividing them into 2 groups on the basis of whether the disease was still active or had subsided at the time of operation, the author found that the mortality of the former group was 9.3 per cent and of the latter 5.3 per cent. Recently these histories have been reviewed; private and unoperated cases, as well as some previously overlooked, included; and the series brought up to date, the total

cent in the second week and thereafter 53 per cent. To avoid these more serious pathological conditions is one of the purposes of early intervention.

There is a general impression that an attack of acute cholecystitis, if treated expectantly, will subside in the large majority of cases. Zininger, however, in observing 54 patients for periods of from 24 hours to 12 days, found that less than two-fifths showed improvement in their condition while the remainder showed no improvement or their condition became worse.

The nub of the question of when to operate is that of the risk of immediate surgery *versus* the risk of delay.

Heuer, Graham, McKenty, and Mentzer advocate early operation and show a lower mortality rate in these cases.

Miller, stimulated by the concurrence of perforation in 2 cases in which operation was being delayed, studied the material at the Massachusetts General Hospital, Boston, and found that in the fatal cases the average duration from the onset of the attack to operation was 15 days while in those with recovery the average time was 8 days. He felt that the expectant plan of treatment should be promptly abandoned if the patient was not definitely improving.

Branch and Zollinger reviewed the material at the Peter Bent Brigham Hospital, Boston, in an article which they designated as a study of conservative treatment. Thirty-four of their series of 229 operative cases were submitted to immediate surgery with a mortality of 14.4 per cent as opposed to the general mortality of 10.4 per cent.

Pennoyer, in a recent paper read before the New York Surgical Society, presented a study of 300 cases from the Roosevelt Hospital, New York, where the surgeons prefer to allow the attack to subside before operating. In order to leave no doubt as to the acuteness of the attack, he included only patients who had had a temperature of at least 101° F (38.3° C.) and a leukocytosis of 12,000 or more. The general mortality was 10 per cent. Among the 59 patients operated on as emergencies the mortality was 25 per cent, and represented half the fatalities in the whole series.

It is but fair to emphasize that in both Branch and Zollinger's and in Pennoyer's series immediate operation was performed in only the seemingly urgent cases, and these were not necessarily

early cases reckoning from the onset of the attack.

Graham, of Toronto, champions a conservative attitude. It is his practice to withhold operation until the temperature is normal unless the condition is becoming worse. He reported a mortality of 5.8 per cent in a series of 68 operative cases.

In the St. Luke's Hospital series, 127 patients were operated upon in the first 24 hours after admission with a mortality of 13 per cent. In the remainder the death rate was 6 per cent. The author concludes that patients with fulminating conditions contribute to a high early mortality, and those depleted by long illness and advanced pathological changes, to a rising late mortality.

After subsidence of the clinical symptoms, there is less risk from intervention than when it is carried out during the acute phase of the condition. Among 164 patients operated on while still febrile, the mortality was 12 per cent, as opposed to 5.2 per cent among 192 who were afebrile.

Discussion—It seems plain from the foregoing that the question of immediate *versus* delayed intervention cannot be settled as yet by the statistical method. In the meantime, it is the opinion of the writer that no rule can be laid down and that each case must be judged on its own merits.

There always will be, of course, urgent cases which will require operation at once and contribute disproportionately to the mortality. However, if a patient is seen in the early stage of the disease and is a good risk, particularly if his symptoms are not severe, a prompt cholecystectomy should not be attended with high mortality, and it forestalls the dangers of later complications.

In the case of the average patient who is admitted with definite, but not urgent,

symptoms, particularly if he is middle-aged or older, it is better to wait if possible for subsidence of the temperature. If, however, improvement is not reasonably prompt, one should intervene without undue delay unless the individual is a poor risk.

Cave summarized his opinion in a paper before the American College of Surgeons in October, 1937, as follows: "In the majority of these cases it is far better that these patients be observed for 24 or 36 hours or even longer, to see whether or not the temperature, pulse rate and blood count will diminish, indicating a subsidence of the inflammatory process. When the temperature remains elevated after 36 to 48 hours, the pulse rapid, and the general appearance is not improving, we do a cholecystectomy or cholecystostomy."

Conclusions—The management of acute cholecystitis cannot be laid down by rule, but calls for individual judgment.

In general, patients whose symptoms have subsided are better risks.

One should be prepared to intervene promptly if progress is unsatisfactory.

Caution is indicated particularly in older patients, who furnish a large proportion of the fatalities.

The experience of F. Glenn⁴⁷ in 170 consecutive cases of patients in the early stages of acute cholecystitis in the past 5 years, lead him to believe that 2 factors, beside the extent of the inflammatory process, have a definite bearing on the outcome of operation in acute cholecystitis. The first of these is the duration of symptoms referable to the gall-bladder before the onset of the acute attack for which surgical treatment is undertaken; the second factor is the age of the patient at the time of operation.

The mortality was not high in cases of uncomplicated, acute inflammation, but

gangrene and gangrene perforation added seriously to the danger of a fatal outcome.

As to the question of complications after operation, there is nothing to indicate that these are influenced by the time at which operation is performed. Much more significant in this respect is the age of the patient and his general condition before operation. The author believes that if time is taken to counteract such conditions as dehydration and cardiac decompensation, and the operation is planned so that it places little additional burden on a sick patient, the incidence of complications after operation for cholecystitis in the acute stage is no higher than after cholecystectomy in chronic cholecystitis.

Treatment—What are the indications for operation in gall-bladder disease?

Enumerated in their order of frequency with the opinion of H. E. Mock, C. F. G. Brown and R. E. Dolkart,⁴⁸ concerning *when* to operate, the following are definite indications:

1. **Cholelithiasis Giving Definite Gallstone Colic**—As a rule, it is advisable to permit the attack to subside or abate before operating. There are cases, however, in which the severe pain persists, the icterus increases, and the patient's condition is growing worse. In this type of acute gall-bladder, early operation is preferable.

2. **Empyema of the Gall-Bladder**—In the acute cases in which the patient has chills and fever and is definitely growing worse, immediate operation is indicated.

3. **Obstructed Cystic Duct with a Markedly Dilated Gall-Bladder**—Such a gall-bladder is often filled with white bile. Infection may develop. At times it becomes difficult to distinguish between empyema and white bile. In some cases the gall-bladder may be so stained and distended with thick dark

bile that it resembles a gangrenous gall-bladder. In other instances the gall bladder may rupture. The condition is definitely surgical and should be operated upon when diagnosed.

4. **Obstructive Jaundice**—This condition is due as a rule to a common duct stone, stricture of the common duct, or to extrabiliary tract inflammation with compression of the duct, either from a subacute or chronic pancreatitis or from an extrabiliary or intrabiliary tumor. Such patients should be observed carefully and be subjected to operation when the obstructive jaundice is lessening or has subsided. Even these patients, however, occasionally have to be operated upon during the acute jaundiced stage to save the patient's life.

5. **Subacute or Chronic Pancreatitis, Usually Accompanying a Cholecystitis**—As a general rule such patients should be placed upon careful medical management. Operation is indicated if the symptoms fail to subside after a few weeks or if the condition is definitely growing worse. In 3 cases which Mock had, the attacks were very acute, the jaundice very marked, and the patients grew progressively worse. All 3 patients were operated upon from the second to the seventh day. In each case the gall-bladder was distended and the pancreas definitely enlarged. In 1 case the swollen pancreas simulated a tumor the size of a baseball. Prolonged drainage of the gall bladder was the operative procedure in all cases. All 3 recovered.

6. **Cholecystitis**—In most instances when this diagnosis is made, the patient is definitely a medical rather than a surgical problem. The majority will readily improve on careful medical management. When no improvement occurs after persistent effort, surgery is justified. Usually a careful investigation of the pan-

creas at the time of the operation will reveal changes typical of chronic pancreatitis.

7. **Gangrenous Gall-bladder**—This is presumably a rare condition, but according to Bailey, of St. Louis, is more common than the profession realizes. It usually results from recurring attacks of cholelithiasis colic, with accompanying gall-bladder inflammation and fibrosis, and this combined with gallstone pressure at the neck of the bladder so interferes with the circulation that an area of necrosis develops. The gangrene may be of only a small portion of the wall or may extend to include most of the organ. Rupture is not infrequent. The mortality rate is very high, especially in the older patients. It is seldom diagnosed except at operation. The threat of this condition developing is a strong argument in favor of surgery in the presence of recurring attacks of gall-bladder disease, unrelieved by medical management.

The indefinite upper right quadrant syndrome that may mean dysfunction of the biliary tract, pancreas, duodenum, or stomach rarely belongs in the field of surgery. In all of these cases the gall-bladder may at times fail to visualize normally. Patients presenting these indefinite complaints should not be subjected to operation without prolonged careful medical management. It should be remembered likewise that there are probably more patients still enjoying comfortable existence with adhesions about the gall-bladder or malformations of this organ than have ever been operated upon for such conditions. The majority of such patients are suffering from functional conditions only temporarily relieved by surgery. It is the surgical treatment of such patients that accounts for the high percentage of unsatisfactory surgical results.

When surgery is performed what is the operative procedure relative to the removal or drainage of the gall-bladder?

It is almost unorthodox for a surgeon to express even a favorable opinion concerning cholecystostomy. In the authors' opinion, however, there are very definite physiological indications for this procedure. They concur with Ivy's view that the gall-bladder that concentrates should not be removed except for very definite indications.

It has been stated by several authors in the past that the drained gall bladder never gives a normal response upon roentgenologic examination. This has been one of the strong arguments in favor of the total removal of all gall bladders. It has swung the majority of surgeons to the "ectomy" as against the "ostomy" side of gall-bladder surgery. In 1927 Spurling and Whitaker examined the gall-bladders of 12 patients by the Graham-Cole test after they had been subjected to surgical drainage. They found that none of the gall-bladders visualized. Moore in 1928 confirmed the findings of these authors. Mock was unable to substantiate these findings. Ten patients upon whom cholecystostomies had previously been performed were studied roentgenologically from 1 to 10 years after operation. Six of the 10 patients showed a normal response to the Graham-Cole test and 8 of them were free from symptoms.

It was further observed by several of the internists on the St. Luke's staff that poor results were being obtained in the patients subjected to routine cholecystectomy. Further studies were therefore carried on by Jenkinson and Foley in the roentgenologic department. Twenty-eight patients who had been treated by cholecystostomy from 8 months to 20 years previously were subjected to a complete series of cholecystographic ex-

aminations. Seven of the patients were males ranging in age from 43 to 78 years. Twenty-one were females between the ages of 32 and 66 years. At the time of operation the gall-bladders were drained from 8 days to 4 weeks. Nineteen of these patients gave a dye response that demonstrated a gall-bladder which filled and emptied normally and gave a homogeneous shadow. Two gave normally functioning gall-bladders with slight defects in contour. Seven were definitely pathological. Twenty-one of approximately 70 per cent of these patients previously subjected to surgical drainage gave a normal response.

Additional studies of Mock on private patients previously cholecystostomized showed that 68 per cent of a total of 40 patients gave a normal gall-bladder visualization. These 2 groups of cases show that gall-bladders which have been subjected to surgical drainage can be objectively demonstrated to be capable of carrying on normal function. The authors believe, therefore, that it is not unorthodox to endeavor to preserve the normal physiological activity of the gall-bladder and biliary tract whenever possible.

In the authors' opinion, cholecystostomy is indicated:

1. Whenever, after exposing the gall-bladder and carefully examining the liver and the pancreas, one finds a definite condition of subacute or chronic pancreatitis is present, with or without cholecystitis or stones, provided the gall-bladder is not so diseased that it must be removed.

It is Mock's experience, and confirmed by the writings of Archibald, de Tarnowsky, and others, that when the gall-bladder is drained because of an existing chronic pancreatitis, prolonged drainage for 6 to 12 weeks is preferable to the usual few days to 2 weeks. The

recurrences and the cases that continue to have upper right quadrant distress most frequently follow a short drainage period. Bile drainage gives the inflammatory changes in the pancreas the best chance for resolution, a condition which usually requires weeks and months.

2 Whenever a few stones, usually cholesterol, are found in a gall-bladder which on close inspection is otherwise negative. Because it has become the container of stones is not a sufficient reason for removing the gall-bladder. The authors are convinced that the percentage of cures in this group is just as high, if not higher, than when the gall-bladder is removed. Furthermore the operation is simpler.

3 In the presence of acute empyema of the gall-bladder, it is the authors' opinion that a quick drainage operation is safer and preferable to the more prolonged cholecystectomy.

When the surgeon exposes the gall-bladder and biliary tract expecting to find stones and fails to find any condition indicative of pathological changes, it is far wiser to back out than to remove or even drain such a gall-bladder. The day is past when this organ should be considered a useless, nonfunctioning vestigial structure.

Cholecystectomy is definitely indicated when a diseased, distended, stone-laden gall-bladder is found. In the more severe forms of biliary tract disease, it still is and probably always will be more frequently indicated than is cholecystostomy. It is not the authors' purpose to condemn or belittle this procedure. Rather theirs is a plea for a more careful individualization of every case instead of subjecting each patient with gall-bladder disease to a routine cholecystectomy.

Conservative Therapy During the Acute Stage of Cholecystitis—Conservative measures employed in the treat-

ment of acute cholecystitis aim to alleviate suffering, to improve the general condition of the patient, and to produce conditions favoring subsidence of the acute process, as outlined by G. S. Bergh.⁴⁹

Alleviation of Pain—Biliary-tract pain results from spasm or distention. McGowan, Butsch and Walters have demonstrated that when biliary colic results from spasm it may be relieved by the administration of **amyl nitrate** or **glyceryl trinitrate**, and we have found that these drugs may be useful in relieving the pain in some cases of acute cholecystitis. In other cases it is necessary to resort to **morphine**, but since that drug causes spasm of the sphincter of Oddi, the relief is entirely central.

Injection of **calcium salts** also has been suggested as a means of relieving biliary-tract pain. Such salts do not have a relaxing effect on the sphincter of Oddi, but Hochman states that the calcium raises the threshold for pain sensibility.

The application of **hot packs** to the abdomen often makes the patient more comfortable. The mechanism of this action is not known, but it is possible that the heat decreases the tone and motility of the gall-bladder.

Improvement of the General Condition of the Patient—Since there may be hepatic damage in cases of acute cholecystitis, **glucose** should be given intravenously to increase the glycogen reserve of the liver. Fluids should be given liberally to combat dehydration. In debilitated patients, especially in the presence of jaundice, **blood transfusions** are of value.

Measures to Produce Conditions Favoring Subsidence of the Acute Process—**Rest** is the most important factor favoring subsidence of acute inflammation. In the case of acute cholecystitis, the activity of the diaphragm, the activity

of the bowel, and the activity of the gall-bladder itself are unfavorable influences.

There is a reflex splinting of the diaphragm and, to a certain extent, intestinal movement is inhibited. Even under a regimen of starvation, however, a certain amount of intestinal activity is nec-

in cases with acute abdominal disorders. In cases of conservatively treated appendicitis with perforation and peritonitis, for example, medication for relief of pain seldom is necessary. Narcotics are avoided in cases in which the nature or extent of the intra-abdominal patho-

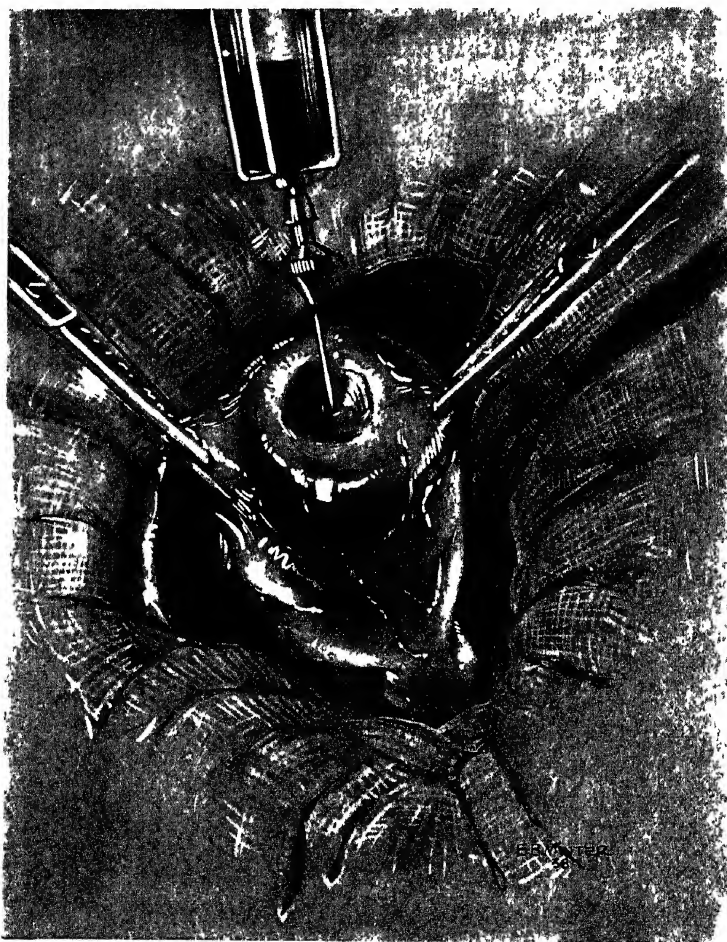


Fig 22—Aspiration of gall-bladder (Am J Surg, 40 198, Apr, 1938)

essary to propel the fairly large volume of secretions which are poured into the upper portion of the alimentary canal. In very acute cases of cholecystitis this factor should be combated by the employment of *continuous suction* applied to an inlying duodenal tube as described by Wangensteen

It has been the author's experience that the use of suction often relieves pain

logical process is still in question, in order that symptoms which might give valuable information concerning the patient's condition are not masked. In severe biliary colic which cannot be relieved by amyl nitrate, however, it may be necessary to resort to opiates.

In less severe cases the patients may be allowed to take carbohydrates by mouth as they do not stimulate motility

of the gall-bladder. Ivy suggests the feeding of cereal gruels, starches, and sugars, especially in the form of corn syrup. He advises adding gelatin to the cereal because its glycin content will not only provide sugar for glycogen forma-

order to keep the gall bladder at rest, therefore, fats, acid fruit juices, and meats, which stimulate the secretion of gastric juice, should be withheld.

Magnesium sulfate or *magnesium oxide* sometimes are given because of



Fig. 23—After incising the fundus, removing the stones and swabbing the gall-bladder mucosa thoroughly with iodine, the gall-bladder is split with scissors down to within 1 cm. of the cystic duct (Am J Surg, 40 197-204, Apr, 1938)

tion, but will improve the detoxicatory function of the liver. He states that *calcium and vitamins A and D* also should be given.

The chief stimulus of gall-bladder contraction is the hormone, cholecystokinin, and the most effective excitants of hormone production are acids and fats acting in the upper part of the intestine. In

the relaxing effect these substances exert on the sphincter of Oddi. There is some evidence to indicate that magnesium causes a slight contraction of the gall bladder as well as relaxation of the sphincter, in which case it might be well to avoid its use in acute cholecystitis.

Biliary antiseptics are apparently of no value, and Ivy states that bile salts

should not be given in cases of acute cholecystitis.

Management After Subsidence of the Acute Process—After subsidence of the acute process a chronic cholecystitis often remains, but this is not invariably the case. The gall-bladder

removal of a functioning gall-bladder are: (1) Slight hepatitis; (2) dilatation of the biliary ducts, and (3) disturbances of function of the choledochoduodenal sphincter mechanism.

On the other hand, if the gall-bladder has been so permanently injured that it

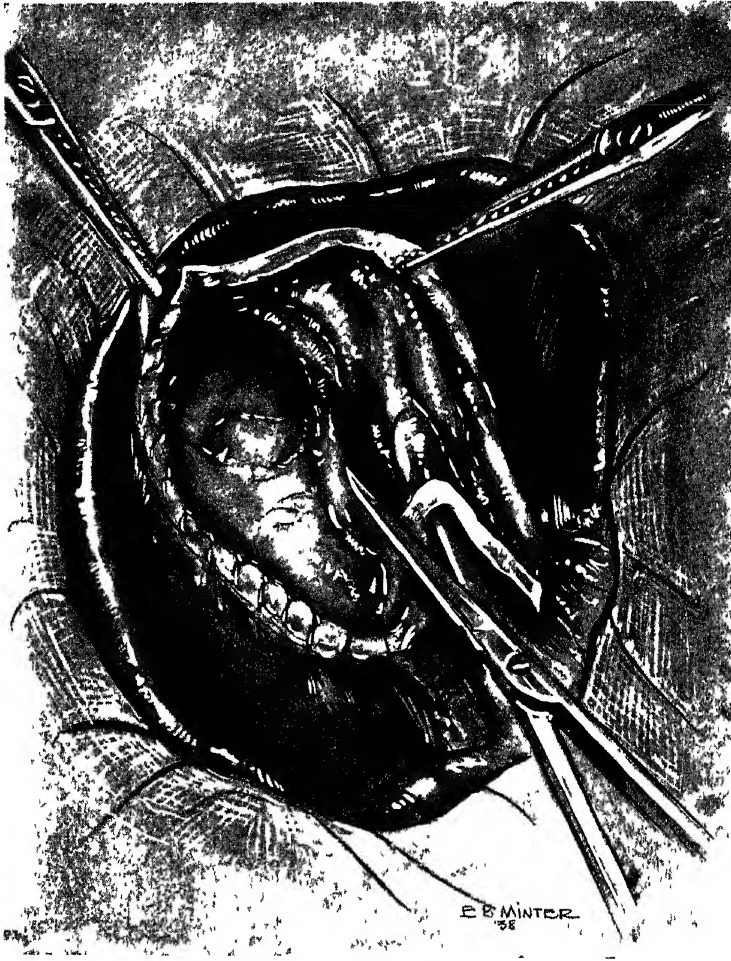


Fig. 24—One-half of the redundant portion of the gall-bladder has been removed and the cut edge sutured with a lock stitch. The remaining half is being cut away and its cut edge will be similarly sutured (Am. J. Surg., 40: 197-204, Apr., 1938).

may resume its normal functions, and since removal of a functioning gall-bladder leads to morphological and physiological changes in the biliary passages and liver, one should not remove a stone-free gall-bladder which concentrates, at least not until medical control has been tried. The changes which follow re-

does not become visible when the Graham-Cole test is applied, a **functional cholecystectomy** has already been performed from the physiological point of view. Consequently, no physiological change or damage would be expected from removal of such an organ, and if it be harboring infection or stones

cholecystectomy is certainly indicated. Furthermore, when it is indicated, surgical treatment should not be delayed too long since complicated pathological processes may develop and greatly increase the risk.

Partial Cholecystectomy—Acute gangrenous cholecystitis is most commonly due to circulatory changes in the gall-

The condition was nonsuppurative in 5 patients, suppurative in 39, and gangrenous in 34 patients. Perforation occurred in 9 cases, and produced a localized pericholecystic abscess in 7, and an acute general peritonitis in 2.

Close observation is recommended in considering the method of treatment of acute gangrenous cholecystitis. For pa-

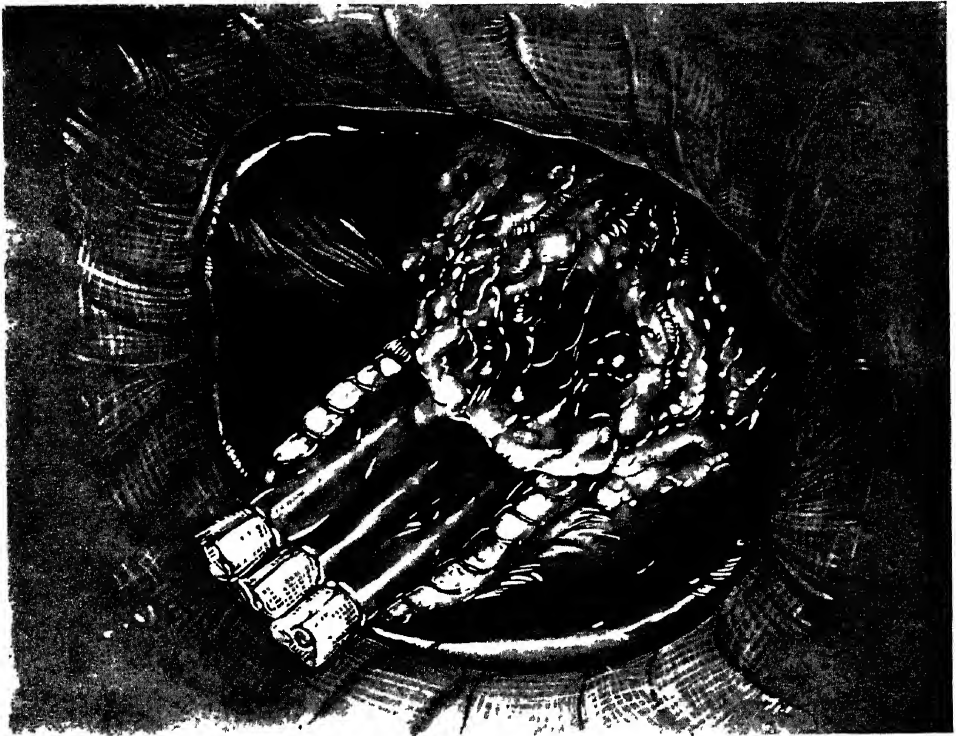


Fig. 25—Cigarette drains in place, holding open the remnant of the gall-bladder attached to the liver. The omentum is placed against the drains to prevent adhesions to the nearby viscera (Am Jour Surg, 40: 197-204, Apr., 1938)

bladder, which occur as a result of the impaction of a stone in the cystic duct. Infarction and infection are usually secondary causes. The incidence reported by various surgeons varies from 12 per cent (Judd and Phillips) to 43 per cent (Estes) of all cases of acute cholecystitis. Perforation occurs in from 0.86 to 5.2 per cent of all cases of this condition treated in the hospital.

W. L. Estes, Jr.,⁵⁰ reviews the cases of 78 patients with acute cholecystitis

patients with symptoms of perforation with spreading peritonitis, immediate surgery is indicated. Careful preparation for surgery is stressed.

If operative treatment is decided upon, the author believes that cholecystectomy, if practical, is the method of choice. In cases of gangrenous and suppurative cholecystitis, a much lower mortality (20.8 per cent) has been shown when partial cholecystectomy has been performed. In this procedure, the free-

lying portion of the gall-bladder is excised, the wall is left attached to the liver, and the cystic duct is not disturbed. In a follow-up study of 42 patients who observed no dietary re-

of a gall-bladder remnant was found in these cases. The mortality rate in this series is compared with that reported in acute cholecystitis, which ranged from 13.5 to 32 per cent.

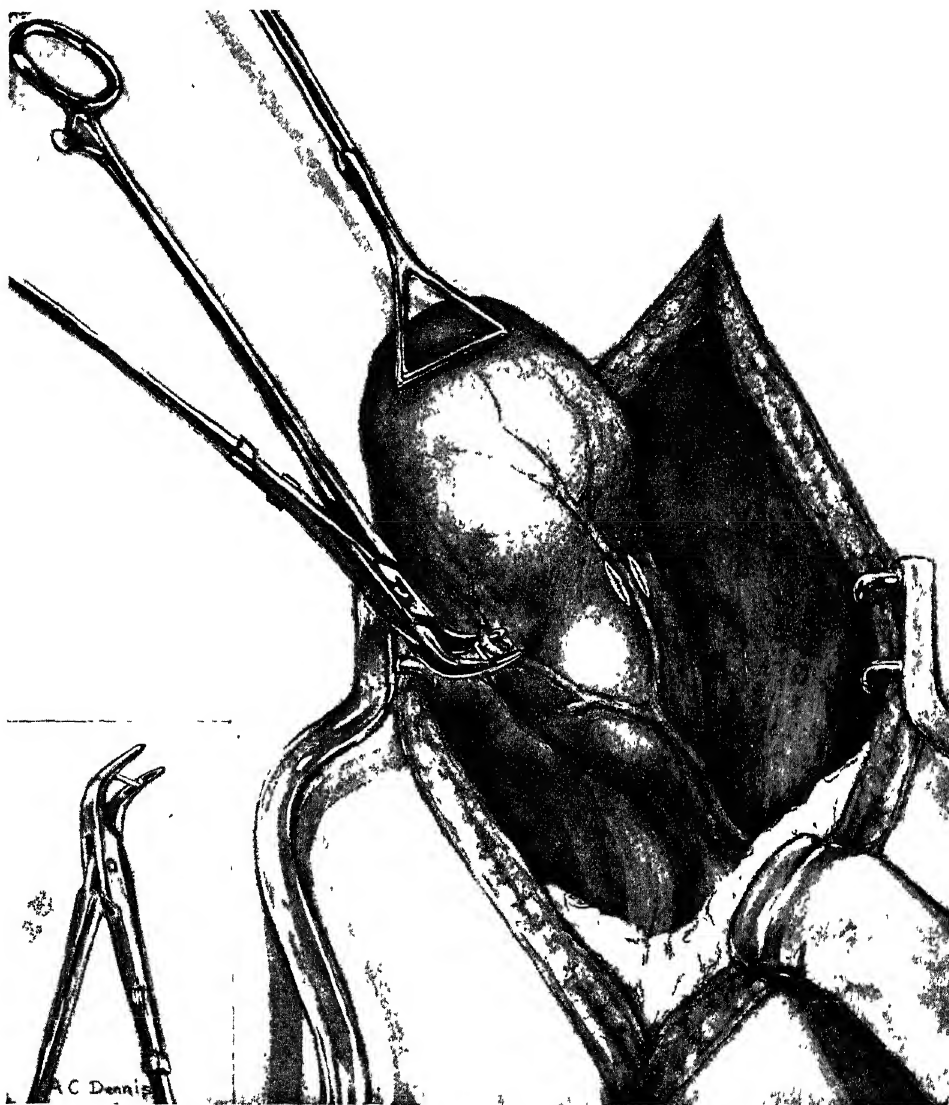


Fig. 26—Dissection of cystic vessels off the wall of the gall-bladder through slits in the serosa, and application of silver clips. One arm of the clip rests flatly in a groove on the dissecting jaw of the clamp. Insert shows the flange on the other arm of the clip which slides along the groove in the other jaw of the clamp and clasps the tissue firmly as the clip is closed. (Am. Jour. Surg., 40: 407, May, 1938.)

strictions, 81 per cent showed no recurrence of symptoms and 11 per cent showed a residual fatty dyspepsia. Four patients were operated upon later for stones in the common duct. No vestige

Cholecystostomy is reserved for the patients who are very bad risks.

The *electrosurgical obliteration of the gall bladder* is discussed by M. Thorek,⁵¹ who states that, if a dry, nonleaking

surface could be substituted for the discharging cavity represented by the bed of the gall-bladder resulting from classic cholecystectomy, it would be an important step. Experimental studies on dogs

service the falciform ligament. So far (August, 1937) 342 operations have been performed by this method in cases of gall-bladder disease including gangrene, empyema and sclerosis. There were 3

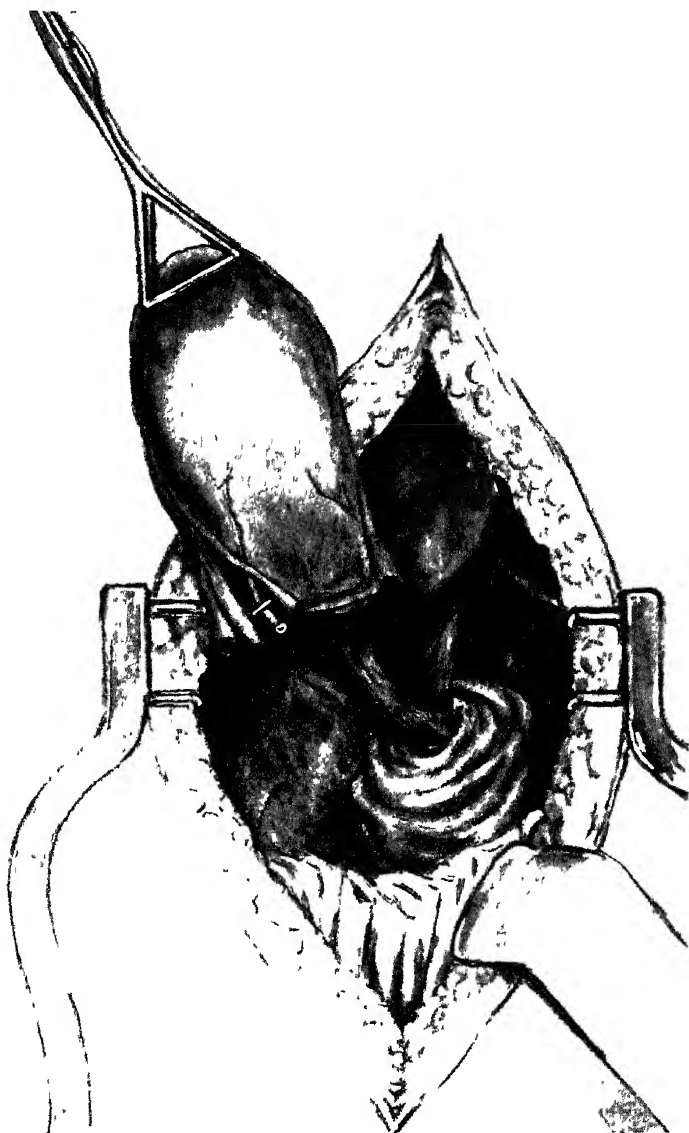


Fig. 27—Peritoneal cuff (somewhat diagrammatic) dissected to junction of hepatic and cystic ducts. The clipped stumps of the cystic vessels have been carried down with the cuff and are a safe distance away. The gall bladder has been dissected from the liver bed and is free to the ducts, which can be easily explored (Am Jour Surg, 40: 407, May, 1938)

and monkeys proved that this can be accomplished by proper electrocoagulation. The tendency of electrocoagulated surfaces to become agglutinated with serous surfaces requires putting into

deaths in the series. One patient succumbed to an undiagnosed chronic subdiaphragmatic abscess some time after operation. Another patient died from massive bilateral pulmonary collapse and

the third from pneumonia about 3 weeks after the operation. Failures and fatalities in classic cholecystectomy are often due to bile leakage, as a result of an inability to obliterate and cover the

compleishes destruction of the entire thickness of the wall of the gall-bladder and, if indicated, also the bed of the gall bladder. The surgeon has under control the degree of penetration he wishes to

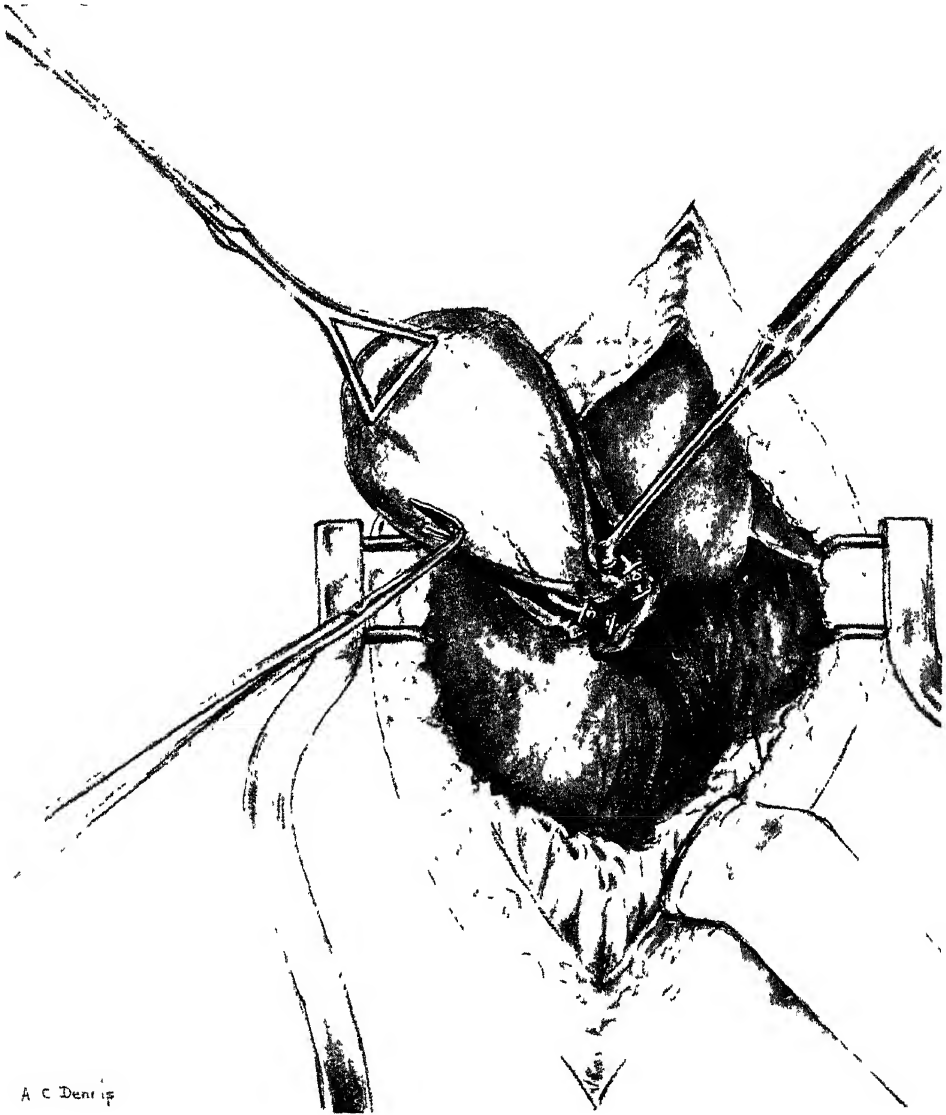


Fig 28—Clips holding cut cystic vessels. On the left are shown right angled scissors dissecting and cutting serosa, on the right is the Walker suction dissector in action (Am Jour Surg, 40 407, May, 1938)

bed of the gall-bladder, and drains invite bile seepage. With this method a prerequisite to satisfactory results is a patent common duct. An occluded cystic duct from any cause is an indication for this operation. The operation effectually ac-

complish. The ligamentum falciforme hepatis is used as a free graft, its serous structure covers sutured or raw surfaces to great advantage, thus reinforcing and protecting the areas concerned against seepage and safeguarding the processes

of repair. Electrocoagulated areas of intra-abdominal organs tend to heal by encapsulation. They do not interfere with wound healing. Therefore drainage is not only undesirable but is distinctly deleterious. Electrosurgical obliteration of the gall-bladder exacts careful technic and meticulous attention to detail.

A subserous cholecystectomy is described by L. R. Whitaker.⁵² The advantages of subserous cholecystectomy are: (1) Facility of operation through a small incision; (2) greater safety, particularly in the region of the cystic and common ducts; (3) quicker and easier recovery of the patient (7 days in bed); (4) fewer complications.

The chief difficulty in subserous cholecystectomy is in control of hemorrhage from numerous small vessels; this can be readily accomplished by the use of modified Cushing silver clips as described.

At about the lower third of the gall-bladder, slits are made through the serosa beside the several branches of the cystic artery. The vessels are dissected up and silver clips applied with the clamp for this purpose.

The serosa and vessels are cut across above the clips and the serosa along the vesicular margins.

The gall-bladder is stripped from above to the junction of the cystic and common ducts, which is palpated. The common duct can be explored and drained through the cystic stump, with a slit into the common duct if necessary.

With the chronic gall-bladder, where a definite, clean stump of cystic duct is doubly tied, and there is no oozing of blood or damage to the liver, drainage is omitted, with the acutely inflamed gall bladder, drains are used.

Results Following Cholecystectomy—The *stoneless gall-bladder* is discussed by C. A. Kunath.⁵³ The author calls attention to a definite dyspepsia

syndrome which includes gaseous indigestion, inability to digest fatty or greasy foods, belching, distention, vomiting, and flatulence, which he believes is largely responsible for the problem of the stoneless gall-bladder. He reports a follow-up study of 100 uncomplicated surgical cases of noncalculous cholecystitis. A similar study for the purpose of comparison was made on 100 consecutive cases of chronic cholecystitis with calculi. The only other operative procedure in both series of cases was simple cholecystectomy.

The age incidence was almost identical in both groups, and averaged 42.3 years in the noncalculous group and 41.9 years in the calculous group. The theory that the noncalculous cases represent the earlier cases in respect to duration of symptoms before admission to the hospital was held with regard to both groups. It is interesting to note that females outnumbered males in both groups, but there were more males in the noncalculous group than in the calculous group.

From the standpoint of the symptoms, it was found that symptoms were always more pronounced in the group with stones. Of the noncalculous cases, 56 per cent gave a history of biliary colic which was accompanied by severe colicky pain requiring hypodermics for relief. It seems that causes other than stones are responsible for the biliary colic.

A careful study of both groups emphasized the fact that the noncalculous showed a greater mortality, a higher postoperative mortality, and only about half as many cures.

Careful analyses were made from the standpoint of pathological changes in the gall-bladder wall of the noncalculous cases. In a general way the percentage of good results rose steadily as the pathological processes in the gall-bladder be-

came more advanced. However, there are some phases of these analyses which are somewhat perplexing. A disturbing factor is the relatively high percentage of cures in the group of patients with normal or nearly normal gall-bladders. Many patients get relief from the symptoms after removal of a gall-bladder showing very little pathological change. It appears that while histological changes may be *nil* or slight, functional or physiological disturbances of the gall-bladder which in no way produce any anatomical change can be present. Therefore, a pathological report can offer no accurate index as to the possible benefit that may result from cholecystectomy.

From the standpoint of cholecystographic evidence, again we meet facts that are difficult to explain. Cholecystography as a means of diagnosing gall-bladder disease has come to be considered an accurate test in a high percentage of cases. As a rule, cholecystectomy is rarely advised when there is a normal cholecystogram. Nevertheless, in this study of Kunath's it appears as a significant fact that 75 per cent of the patients with normal cholecystograms were cured. It is possible that incidental appendectomy is responsible for the cures in this group with normal cholecystograms. One is obliged to concede that while cholecystography is a contributing factor in the diagnosis of gall-bladder disease, it cannot be entirely relied upon either for diagnosis or prognostic purposes following cholecystectomy. Kunath expresses the opinion which other investigators before him, notably Burden, Sanders, Judd, Palmer, Graham, and Mackey, have expressed; *i.e.*, that an analysis of pre-operative symptoms is probably of greater value in estimating the probable benefits to be derived from cholecystectomy than the cholecystographic evidence or the pathological report. The trend now is to

regard the presence of definite biliary colic as the most dependable indication for cholecystectomy, as well as the symptom most likely to be relieved by this means. Eighty-six per cent of the patients with colic under investigation were cured. Of the cases in which vague dyspeptic symptoms were present prior to operation, only 33 per cent was cured. Moreover, the dyspepsia syndrome developed postoperatively in 38 per cent of the cases in which it was absent preoperatively. Observations such as these seem to favor the view that the dyspepsia syndrome is more closely related to non-function of the gall-bladder than to disease of the gall-bladder.

Kunath believes that the majority of the cases which showed no improvement must be explained on a basis of physiological change or altered function. He ventures the opinion that there probably is a large group in every series of non-calculous gall-bladders lying on the border line between organic and functional disease. It is difficult to diagnose these cases and the results after cholecystectomy are apt to be disappointing. A better understanding of the physiology of the biliary tract will doubtless help to remove much of the doubt and disappointment that are now so frequent in the treatment of the noncalculous gall-bladder.

The Heart in Gall-bladder Disease

The condition of the heart in 65 consecutive cases of disease of the gall-bladder and the biliary tract was determined by S. M. Laird.⁵⁴ There were 58 women and 7 men. Fifty of the patients had a clinical cardiac lesion. Of the 65 patients, 24 were regarded as obese. This suggests that the obesity, if a factor, is not the whole explanation of the presence of cardiac lesions in these cases of disease of the gall-bladder. Fifty patients were

followed up or were under observation until death occurred. Operation was performed in 40 and 13 of these had cardiac manifestations. Cholecystectomy produced a cure of the symptoms of gall-bladder disease in 78 per cent of cases in which this operation was performed and appeared to be a satisfactory measure for obtaining amelioration of the cardiac manifestations occurring in cases of disease of the gall-bladder. The presence of similar cardiac conditions in cases of disease of the gall-bladder does not constitute a contraindication to cholecystectomy. Fatal pulmonary embolism occurred as a postoperative complication in 5 per cent of the cases. There was some evidence to suggest that the longer disease of the gall-bladder is permitted to exist, the greater is the possibility of cardiac manifestations making their appearance. The incidence of lesions of the heart in cases of disease of the gall-bladder was not influenced by the presence of jaundice. Coronary artery thrombosis occurred in 12 per cent of the cases and on occasion may present difficulty in differential diagnosis. The electrocardiographic evidence was inconsistent in many cases of myocardial insufficiency when compared with the clinical condition of the patient, but was of great value in cases in which coronary artery thrombosis had occurred.

Hepatorenal Syndrome

The various clinical and pathological aspects of the so-called hepatorenal syndrome occurring after operations upon the gall bladder and biliary ducts as reported in the literature are discussed by J. H. Garlock and S. H. Klem⁵⁵. Many of the reports were found to be wanting in post-mortem studies. Those that include necropsy examinations present a curious lack of uniformity of the pathological picture, which raises the question

of why one case presents minimal findings at autopsy, while another with the identical clinical picture may exhibit extensive hepatic and renal degenerative changes.

A possible explanation for this considerable variation in degree and extent of the pathological findings is suggested. It seems possible that many of the patients have some degree of kidney damage before the surgical attack on the biliary system, with a small margin of safety from the standpoint of renal reserve. This impairment may not be apparent or demonstrable by any known laboratory methods. Following the operation upon the diseased biliary tract, with its associated surgical trauma and the greatly altered physiology that must necessarily follow, the already impaired kidneys are unable to cope with the additional load thrown upon them and soon break down completely. The clinical picture, with the relatively free interval of 5 to 10 days after operation, suggests confirmation of this thought.

A case is reported in detail in which, 5 days after operation for a calculous gall-bladder and bile-duct disease, there followed a clinical course characterized by progressive asthemia and uremia with terminal icterus. Death occurred on the thirteenth postoperative day. The post-mortem findings, in contrast to the severe liver and kidney changes reported in the literature, consisted only of mild parenchymatous degeneration in these organs, and acute cholangitis. These changes certainly could not be held responsible for the clinical course of the patient. The kidneys, however, showed some focal interstitial inflammation, manifested by nests of lymphocytes, plasma cells, and infrequent polymorphonuclear leukocytes within the stroma of the medulla. In addition, there was a striking glomerular lesion. This consisted of an increase

in the size of the glomeruli, which was due to prominence of the intercapillary connective-tissue framework which appeared spongy, as if distended by fluid. There was no increase in the cellularity of the malpighian corpuscles. This glomerular picture bore a strong resemblance to the acute intercapillary glomerulonephritis described by MacCallum and considered by him to constitute the initial stage of the chronic condition known as glomerulonephritis.

In conclusion, the authors have formed the opinion that no logical or satisfactory explanation of the so-called hepatorenal syndrome has as yet been offered. Although many authors believe it to follow surgery of the biliary tract only, the same syndrome has been known to follow operations upon the gastrointestinal tract and also extensive cutaneous burns, conditions known to be closely linked with disturbances of the protein metabolism.

Carcinoma of the Gall-Bladder

A comprehensive study of 48 cases of carcinoma of the gall-bladder, in the period from 1915 to 1935, has been given by W. A. Cooper.⁵⁶

Incidence—The apparent increase in the frequency of carcinoma of the gall bladder roughly parallels the increase in frequency of operations on the gall-bladder. In 1500 operations on the gall-bladder, the surgical incidence of carcinoma was 3 per cent, while the autopsy incidence was 0.61 per cent in 2041 cases.

Most of the patients were between the ages of 50 and 60 years, and it was noted that inflammatory disease of the gall-bladder was most common between the ages of 40 and 50 years. Seventy-seven per cent of the patients were women, which is in agreement with other reports, the ratio being, roughly, 4 women to 1 man.

Etiology—Of the various etiological factors, chronic irritation incident to cholelithiasis and infection is the most constant finding. Stones were found in 79 per cent of the patients, and 48 per cent gave a history of colic of long duration. Malignant degeneration of benign papillomas of the gall-bladder is also possible.

Pathology—Pathologically, the disease may be divided into 2 groups, adenocarcinoma and squamous carcinoma. The former group is subdivided into: (a) Papillary adenocarcinoma, 12 per cent; (b) infiltrating adenocarcinoma, 56 per cent, (c) scirrhous adenocarcinoma, 25 per cent, and (d) mucous adenocarcinoma, 12 per cent.

Inflammation and chronic mechanical irritation produce a variety of reactions in the gall-bladder, and the types of reaction seems to determine to some degree the type of lesion formed. If the submucosa is more responsive than the mucosa, the resulting papilloma may be composed chiefly of connective-tissue elements covered with epithelium. Should the response be an overgrowth of epithelium, simple benign papillomas develop.

The appearance of squamous-cell carcinoma in the gall-bladder is explained on the basis of metaplasia. One example was seen in the present series. Clinically, this type may resemble scirrhous adenocarcinoma.

Carcinoma may occur in any portion of the epithelium of the gall-bladder, but it is estimated that from 80 to 90 per cent originates in the fourth of the mucosal area represented by the dome and neck of the gall-bladder. This distribution again suggests the importance of calculi as an etiological factor. The site of the tumor obviously influences the course of the disease and clinical picture.

In general, carcinoma of the gall-bladder disseminates by local extension, lym-

phatic metastases, and blood-borne metastases. Local extension is by far the most common method of spread, and the liver is involved earlier and more frequently than any other organ.

In 52 per cent of the patients, there was a history of gall-bladder disease of long standing, and in 70 per cent of those in which no such history was elicited, stones were found. After the onset of carcinoma, the clinical course is usually modified by symptoms of referable to the tumor and its growth. The symptoms and signs, and their incidence in this series is as follows: Pain in 69 per cent, loss of weight in 95 per cent; anorexia in 85 per cent; tenderness in 73 per cent; a palpable mass in 50 per cent; a palpable edge of liver in 50 per cent; jaundice in 48 per cent, and vomiting in 45 per cent. Leukocytosis, anemia, and chills and fever occurred less frequently. There were 7 atypical cases. Four of the patients had symptoms of obstruction of the common duct, 2 presented duodenal obstruction, and 1 had a condition which resembled hydrops of the gall-bladder.

Diagnosis—The diagnosis of carcinoma of the gall-bladder is difficult to establish with certainty. A constant dull aching pain in the epigastrium or right upper quadrant, persisting over a period of weeks, is one of the most valuable features in the differential diagnosis. Cholecystograms are seldom said to be of aid. In 17 cases in which cholecystograms were made, a positive diagnosis of carcinoma of the gall-bladder was not made by roentgen examination.

Treatment—The results of treatment are not encouraging. Operations which consisted of *exploratory laparotomy* with removal of tissue for biopsy, *cholecystectomy*, *cholecystostomy*, and *gastroenterostomy* were performed in 45 cases. Five patients were free of metastases at operation. One patient who was

TABLE 3
COMMON DUCT STONES

	Exploration		Stones Found		Total Cases
	Number	Per Cent	Number	Per Cent	
1910 to 1926	96	15.0	52	8.4	619
1927 to 1928	91	32.7	38	13.7	278
1929 to 1930	49	35.8	22	16.1	137
1930 to 1931	61	42.5	30	21.0	138
1931 to 1932	45	38.0	22	19.0	118
1932 to 1933	52	46.0	24	21.2	113
1933 to 1934	42	35.0	21	17.6	119
1934 to 1935	48	35.0	17	12.0	143
1935 to 1936	67	46.2	28	19.3	145
1936 to 1937	74	40.2	23	14.4	159
1937 to 1938	95	50.8	34	18.3	187

known to be alive and well 2 years following operation was subsequently lost from observation. The remainder succumbed at operation or shortly thereafter.

The author agrees with Graham that the most rational attack on this disease is its prevention by early removal of the gall-bladder in all cases of cholelithiasis.

Common Duct Stones—Earlier operation upon patients for gallstones would cut down the number of patients in whom common duct stones are now found, and this is the logical approach to improve the results of surgery for cholelithiasis. According to F. H. Lahey,⁵⁷ many patients have in the past and are still having gall-bladders removed and common duct stones left behind.

If we wish to remove all of the stones in the gall-bladder and biliary tract, the common and hepatic ducts must be explored in approximately 50 per cent of the cases and in approximately half of these cases stones will not be found.

The condition of the wall of the gall-bladder and the character of the bile within it are valuable criteria as to whether or not the common and hepatic ducts should be opened and explored.

Inspection of bile in a hypodermic syringe by transmitted light gives excel-

lent evidence as to the probable presence of infection or stones within the main bile ducts and the need for their exploration and drainage.

Technical measures are discussed which have to do with the safety of the operation and with the length of post-operative drainage.

Finally, no operation for gallstones offers the patient the highest percentage of relief of symptoms, the lowest percentage of complications and the lowest percentage of complications and the lowest ultimate mortality unless it not only removes the stones within the gall bladder and the gall-bladder itself, but also assures the surgeon and the patient that any possible stones within the common and hepatic ducts have also been removed, and that that structure is, to the greatest possible extent, relieved of its associated infection by drainage.

According to G Zopff,⁷⁸ in the last 3 years 202 cholecystectomies were performed at the Heidelberg clinic. During the same period, 45 (18.5 per cent) patients were readmitted to the clinic because of recurrence of symptoms. The original operation was performed from 6 months to 12 years before. Only 11 had their original operation at the Heidelberg clinic. On reoperation a stone was found to be present in the extrahepatic bile passages in 23 (51 per cent), or 9.3 per cent of the total number of patients operated on during the same period. Inflammatory alterations were responsible for the symptoms in 11 (24.5 per cent). Eight patients presented mechanical disturbances either in the biliary tract or in the intestine. Dyskinesia was assumed to be the cause in 3 (6.7 per cent). Enlargement of the periportal lymph nodes was found to be the cause in 2 cases. Carcinoma at the hilus of the liver was observed in 1. There were 3 types of inflammatory alterations. Those

of the bile passages, late abscesses, and inflammation of the head of the pancreas. The patients in whom the symptoms were due to inflammation of the bile passages responded well to conservative treatment, which consisted of the passage of the *duodenal sound* and flushing with 40 per cent *magnesium sulfate*. There were 4 instances of late abscesses which had developed in cases of neglected cholangitis. More than 50 per cent of recurrences were due to a stone. The author believes that most of the recurring stones are those overlooked at the time of the original operation, although he does not reject the possibility of formation of new stones in the extrahepatic bile passage. In proof of the latter contention, the author cites 3 cases in which stones were removed from the common bile duct and in which there was congenital absence of the gall-bladder. The author likewise had seen 2 consecutive recurrences of stones in the common bile duct. He stresses Enderlen's advocacy of an early operation for gallstones. The stones may lie a long time in the common duct without producing symptoms, though they prepare the ground for a recurrence after a cholecystectomy. Among 202 cholecystectomies, stones were removed from the bile passages in 28 cases (13.9 per cent). Because of a definite increase in mortality when the choledochus is opened, roentgenologic investigation of the patency of the duct during the operation as proposed by Mirizzi, was adopted in the Heidelberg clinic. In addition, they have attempted to locate the stone by transillumination of the duct. The favorite seat of a recurring stone is the physiologic enlargement of the duct just above the sphincter of Oddi, giving rise to symptoms of a valve stone with or without involvement of the pancreas. The diagnosis of the presence of a stone in the common duct constitutes an indi-

cation for operation. Choledochotomy and the removal of the stone were considered sufficient in the presence of a patent duct. Drainage was practiced only in the presence of severe inflammation, icterus and white bile. The author considers systematic medical aftertreatment an important prophylactic measure in preventing recurrence of symptoms

Glyceryl Trinitrate

Therapeutic Value in Biliary Colic and in Postoperative Phase of Biliary Tract Disease—The histological study of the extrahepatic biliary system revealed more abundant muscle tissue in the fundus and neck of the gall-bladder wall than at the site where the cystic duct approached the common duct. The so-called "collum cysticus" sphincter was not identified. The hepatic and common bile ducts consisted mainly of fibro-elastic tissue with scattered strands of muscle tissue down to the region of the ampulla and the sphincter of Oddi, where nonstriated muscle again appeared and reached its maximum thickness. It formed a sphincter which mechanically guarded the entrance into the duodenum, and which, clinically, induced a typical sphincteric syndrome

Atropine, morphine and atropine, epinephrine, ephedrine, magnesium sulfate, and fats, such as cream or olive oil, were found to be effective, either individually or in combination, in relieving only a small percentage of cases.

R. R. Best and N. F. Hicken⁷⁹ experimented with the use of *glyceryl trinitrate* in 3 groups of cases

1. In ordinary biliary colic when the gall bladder had not been removed, glyceryl trinitrate gave relief in some cases and was a failure in others

2. In the cases of patients whose gall-bladder had been removed some years previously but who still had attacks of

biliary distress, glyceryl trinitrate gave immediate relief when other antispasmodics had failed. With the use of this drug it was noted that small stones were released from the common duct, there being no relief if the stones were too large to get through the choledochus sphincter or were caught in a narrowed portion of the common duct.

3. In cases of patients with spastic biliary dyssynergia, who were carrying common-duct tubes or catheters and in whom the distress was caused by a disturbance of the sphincter of Oddi, glyceryl trinitrate often brought about immediate cessation of pain when the combination of morphine and atropine had not given the desired relief. Glyceryl trinitrate may be used in combination with morphine, as the relaxing effect of the glyceryl trinitrate on the sphincter seems to be greater than the spastic effect of the morphine on the duodenal wall. Atropine appears to give the most relief if the gall bladder and cystic duct are involved. When there is an active pathological condition, atropine or a combination of morphine and atropine has not always been found to be effective

The greatest success with the use of glyceryl trinitrate has been obtained in those cases in which rather typical distress recurred following the removal of the gall-bladder

Bile Salt Therapy in Gall-bladder Disease

H. Doubilet and his associates⁶⁰ report 38 cases of pain and dyspepsia after cholecystectomy, in the majority of which relief was obtained by a *fat-free diet* and by an adequate intake of *bile salts*. Certain exceptions must be observed. If a choledochal stone is present, the increased flow of bile following the administration of bile salt results in an accen-

tuation of symptoms or even the appearance of jaundice. Any condition, such as partial stricture, malignant growths or chronic pancreatitis, which would diminish the diameter of the common bile duct could cause an increase in symptoms after treatment with bile salt. The presence of gastric hyperacidity renders treatment difficult. In such cases the frequent

disappearance of the difficulty in digestion and the improvement in intestinal peristaltic action all tend to eliminate the tendency to gastrointestinal spasm. In support of this, it has often been noted that the relief of constipation only by the ordinary saline cathartics is occasionally of some assistance in the improvement of painful symptoms. The removal of a



Fig. 29.—An apparatus for measuring changes in intraduodenal pressure. (Am. J. Surg., Gynec. & Obst., 66: 979-987, June, 1938.)

attacks of pain seem to be due to the recurrent spasm of the sphincter of Oddi. The addition of *atropine* and *alkalis* to the therapy is of great assistance. The neurotic patient is also difficult to treat, since any emotional upset brings on an attack of pain. This is apparently due to a spastic condition of the gastrointestinal tract which involves, among other sphincters, the common duct sphincter as well. It would seem that the increased flow of bile from the liver, the

functioning gall-bladder containing a few stones should be deprecated on general physiologic principles. Medical therapy should be attempted before operation is advised. However, the treatment of patients suffering from disease of the gall bladder cannot be condensed to a few directions, but, if one keeps constantly in mind the known physiologic principles of the biliary and gastrointestinal tracts, one can achieve considerable success in the therapy of disease of the gall-bladder.

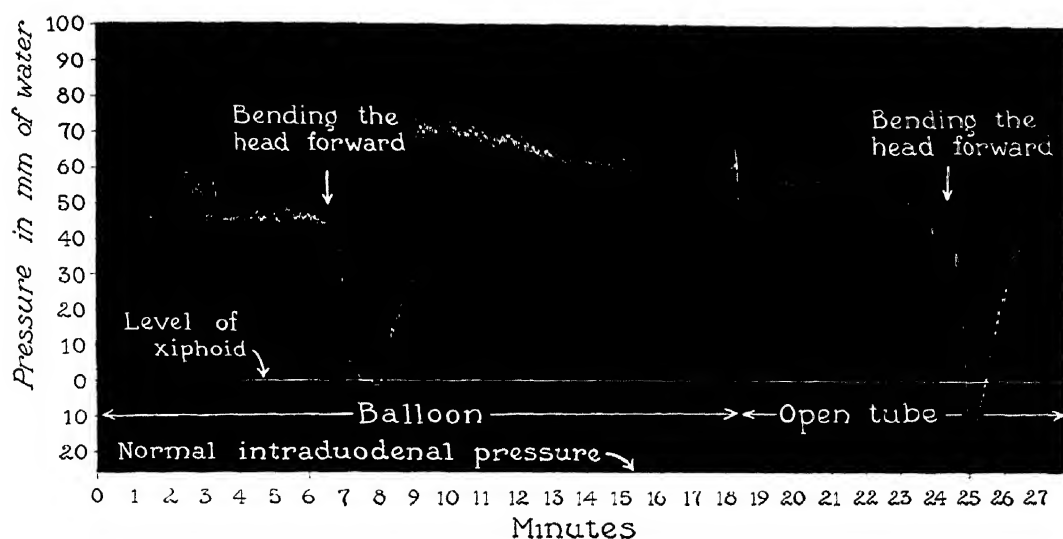


Fig 30—Tracing showing reduction of intraduodenal pressure on bending the head acutely forward. In this case 2 tubes were inserted into the duodenum, 1 open and 1 with a rubber bag on the end. The pressure tracing from each is essentially the same. (Surg., Gynec. & Obst., 66: 979-987, June, 1938.)

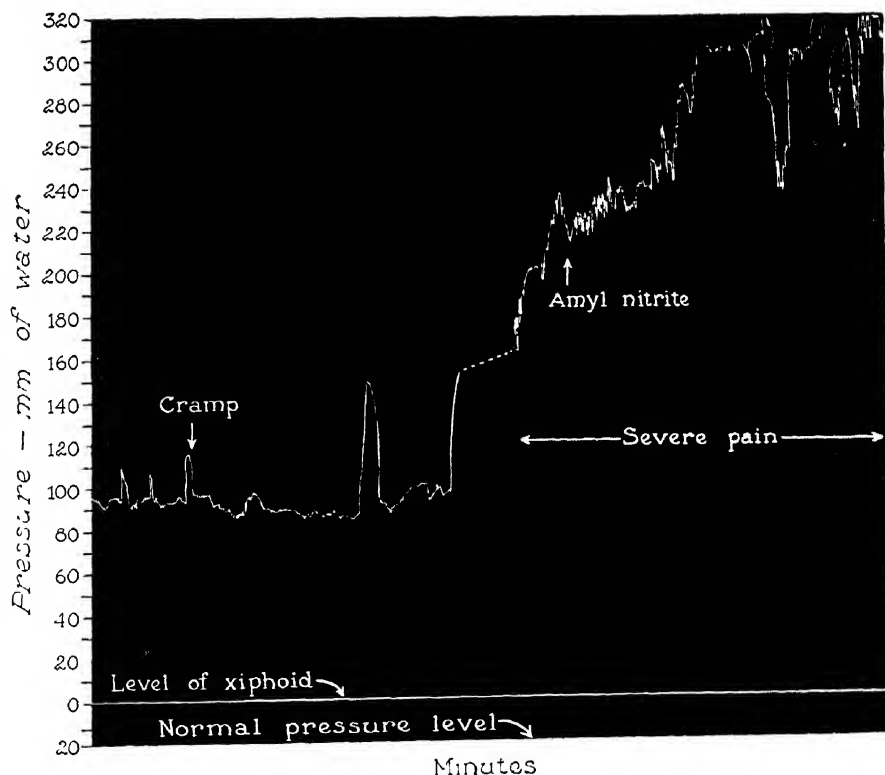


Fig 31 — Tracing obtained in a case in which the patient had a high resting value for intraduodenal pressure, showing a further increase in pressure during an attack of pain. (Surg., Gynec. & Obst., 66: 979-987, June, 1938.)

Relation of Spasm of the Second Portion of the Duodenum to Biliary Colic

A method for studying the activities of the duodenum has been presented which consists of measuring changes in pressure in the duodenum by means of an ordinary open Sawyer duodenal tube and a water manometer by J. M. McGowan, P. A. Knepper, W. Walters and A. M. Snell⁶¹ After injecting a mix-

Resting values for intraduodenal pressure were determined in 3 groups of cases. Patients suffering from repeated attacks of postcholecystectomy biliary colic capable of relief by nitrites were found to have intraduodenal pressures of from minus 35 to minus 50 mm. of water. In normal subjects, pressures of minus 30 to 0 mm of water were encountered. In individuals with intractable postcholecystectomy colic, not

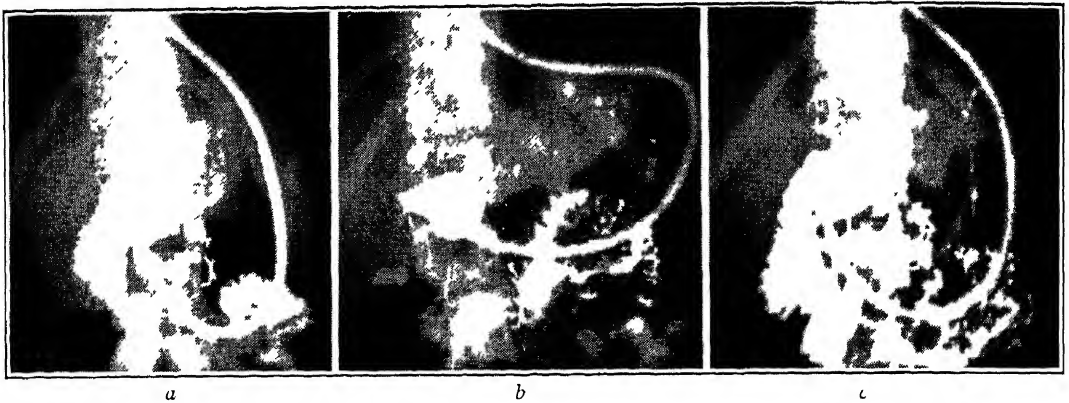


Fig 32—Duodenum of a patient with a persistently high intraduodenal pressure, *a*, Resting state, showing obstruction in third portion and some spasm in second portion, closing it partially, *b*, same patient 10 minutes after administration of morphine sulfate, the second portion of the duodenum having been closed completely by more spasm, and *c*, same patient following inhalation of amyl nitrite, the duodenum is again relaxed, but there is a persistent narrowing in the second portion and a persistence of obstruction at the duodenojejunal junction (Surg, Gynec & Obst, 66 979-987, June, 1938)

ture of barium and water directly into the duodenum through the tube, roentgenograms were taken of the duodenum under various phases of changes in pressure. Morphine produced an increase in intraduodenal pressure due to spasm of its second portion. Amyl nitrite relaxed this spasm. Roentgenograms taken by simultaneously injecting brominol into the common bile duct through a previously inserted T-tube, and by injecting barium into the duodenum through a Sawyer tube, showed that the spasm of the duodenum produced by morphine seems also to involve the lower end of the common bile duct.

relieved by nitrites and presenting roentgenological evidence of obstruction of the third portion of the duodenum, the resting values for intraduodenal pressure were between plus 30 and plus 100 mm of water.

In patients with abnormally high intraduodenal pressures, stimulation of the carotid sinus or moderate doses of insulin produced a moderate reduction in pressure; this was of a temporary nature, however, and did not give any constant relief from pain.

The evidence presented indicates the importance of studying duodenal motility in cases of intractable biliary colic

and the desirability in such cases of searching for some organic change in the common duct, sphincter, or in the duodenal wall itself.

Common Duct Stones

Nonoperative Management of the Remaining Common Duct Stones—During the last few years R. R. Best and N. F. Hicken⁶² have taken many immediate cholangiograms at the operating table and have adopted the rule of making delayed studies in all cases of

the past they have not been sufficiently cognizant of the series of events which takes place in the common duct after surgical treatment of the biliary tract. It can be fully appreciated only by those who have determined the postoperative status of the common duct through cholangiography. With this situation in mind, and fully aware of the mortality attending secondary attacks on the biliary tract, the authors have attempted to dislodge some of these foreign bodies by various nonoperative measures.

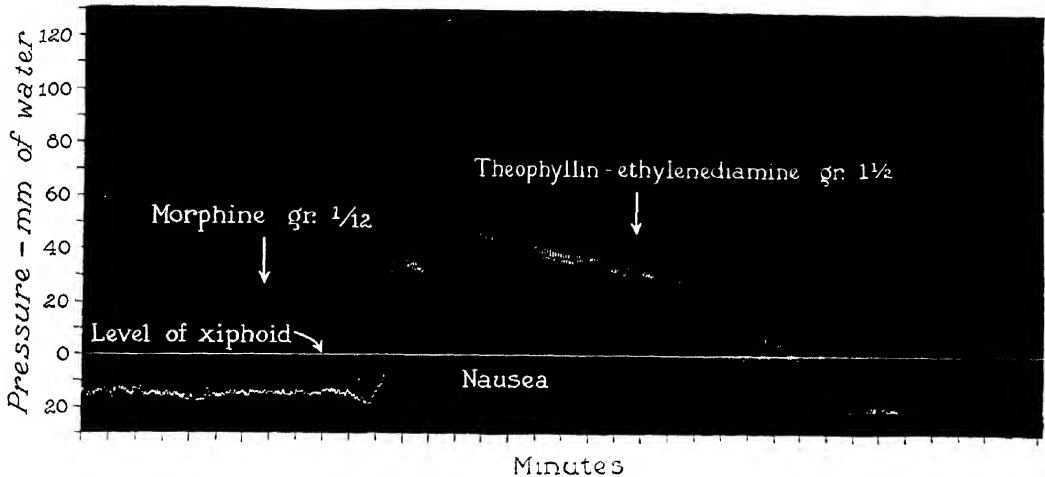


Fig 33—Tracing of intraduodenal pressure in a normal person, showing effects of administration of morphine sulfate (Surg, Gynec & Obst, 66 979-987, June, 1938)

common duct drainage or biliary fistula. These series of follow-up cholangiograms have added inestimably to knowledge of the pathologic physiology of the extrahepatic biliary tract.

Much to the authors' surprise, they have not infrequently found delayed cholangiograms to reveal stones or foreign bodies such as blood clots, organized debris or inspissated bile in common ducts which were thoroughly explored by palpation, probing, scooping, irrigation and suction at the time of operation. Thus it has been forcibly brought to the authors' attention that these foreign bodies may be left within the duct or may be washed down from the liver. In

The authors have been able to depict apparent foreign bodies in 2 other common ducts by postoperative cholangiograms, but these defects were inconstant in appearance as well as irregular in shape. It is highly possible that they were small blood clots or lumps of inspissated bile which were later dislodged. In any event, they disappeared under the described treatment. In a recent case, although no stone could be palpated, the postoperative cholangiogram revealed a large stone within the common duct. Repeated efforts to dislodge it have been ineffectual, and ether has also failed to break it up. Another operation is to be advised.

Suggested Technic for Removal of Remaining Common Duct Stones—When a stone is located in the common duct by delayed cholangiography, the following 3-day regimen is begun. On the first day a $\frac{1}{100}$ grain tablet of *glyceryl trinitrate* is placed under the tongue 3 times during the day, on the second, $\frac{1}{100}$ grain of *atropine* is given either by mouth or hypodermically 3

of warm sterile olive oil or lipoidine is instilled into the common duct. If the patient does not complain of distress, the tube should be clamped off during this course of treatment except for a 30-minute period after each instillation. In order to maintain an increased intra-ductal pressure, 3 or 4 tablets of *decho-lin* or *procholon* are given 4 times a day

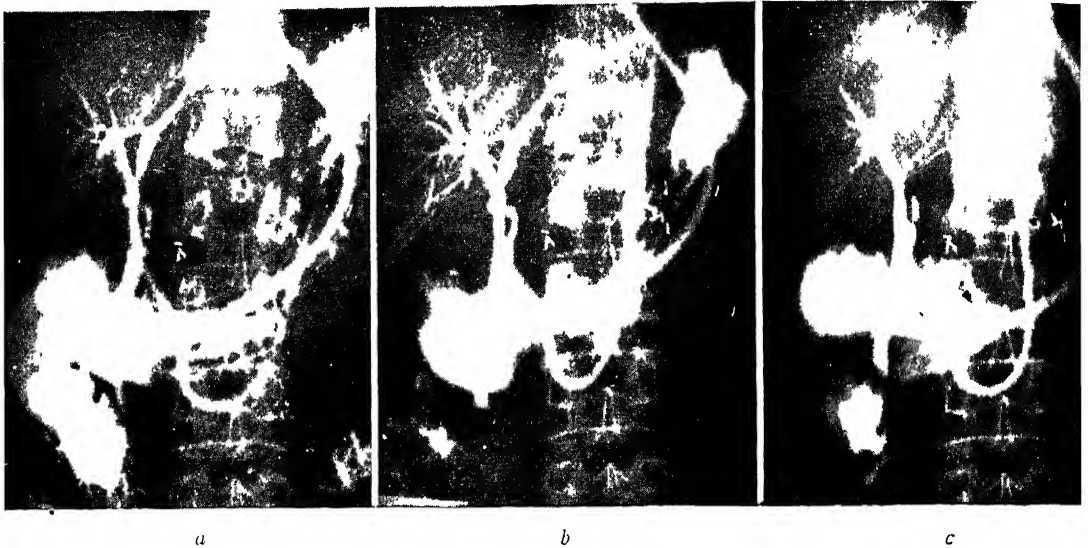


Fig. 34—Serial roentgenograms after simultaneous injection of the common bile duct with brominol through a T-tube and of the duodenum with barium: *a*, at rest; *b*, 10 minutes after administration of morphine sulfate, showing spasm of duodenum and reflux of medium into the finer radicles of the biliary tree; and *c*, after inhalation of amyl nitrite, showing relaxation of duodenal spasm and decrease in amount of medium in the bile ducts. (Surg., Gynec. & Obst., 66: 979-987, June, 1938.)

times, and on the third the administration of glyceryl trinitrate is repeated. Each morning the patient is given 2 drachms (8 Gm.) or more of *magnesium sulfate* in warm water and each evening at bedtime 1 ounce (30 cc.) of *olive oil* (preferably) or *thick cream*. The common duct is gently irrigated once a day through the T-tube, catheter or fistula, with warm physiologic solution of sodium chloride, and after as much of this as possible is removed by syringe or by permitting the tube to drain for 5 minutes, from 10 to 30 cc.

This treatment may be repeated after a few days' rest, and, as in the first case reported, it may be repeated as many as 10 times over a period of 2 months. It may prove rather debilitating at times and care must be taken not to exhaust the patient.

The question arises as to the indications for this form of treatment when no fistula or arrangement with a catheter exists. If obstruction is complete, there may be danger of hastening hepatic destruction by increasing the biliary pressure. In several cases in which obstruc-

tion has not been complete, the authors have ventured to use the treatment, omitting the irrigations, with no evident harmful effects and with definite improvement or complete alleviation of the biliary condition. The authors have recovered no stones from the stools as yet in such instances, but the patient's search for stones at home is not so exacting. One should always be aware of the potential danger in such treatment, however, and until further investigative

surgical management of routine biliary tract disease, exclusive of jaundice.

Complications of Gall-bladder Surgery

The complications of gall-bladder surgery include all the possibilities for disturbances following any laparotomy. However, H. M. Clute and H. Albright⁶³ consider only those most commonly related to surgery in this area. Persistent fever usually indicates wound infection,

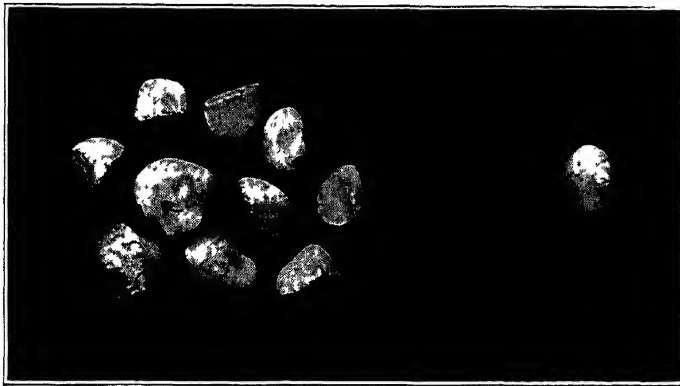


Fig. 35 (Case 2)—The group of 10 stones was recovered from the stool after the first course of treatment. The single stone was recovered after the second course. (J. A. M. A. 110:1260, Apr. 16, 1938.)

studies have been made, the dehydrocholic acid products should be cautiously prescribed when there is any degree of jaundice with supposition of stone in the common duct. If the jaundice is marked, with acholic stools, great damage might be done to the liver, and dehydrocholic acid should definitely not be prescribed. However, in all cases following cholecystectomy in which jaundice does not exist, the authors now place the patient on the described 3-day regimen about 2 weeks after operation in an effort to flush the biliary system thoroughly and remove small stones, mucous plugs, inspissated bile and organized débris, thus lessening the incidence of postcholecystectomy difficulties. This particular regimen is now being used in the non-

cul-de-sac abscess, or subphrenic abscess. Inspection, palpation, and probing of the wound are necessary to demonstrate or exclude infection in the wound. Repeated rectal examinations may demonstrate a boggy collection of pus in the *cul-de-sac*. This should be evacuated when fluctuation is present. Subphrenic abscess appears more commonly on the right side but it was found on the left side in 2 instances in the authors' experience. It should be suspected: (1) When post-operative x-rays show a high fixed diaphragm with an obliterated or narrowed costophrenic angle; (2) when the x-rays show either pleural fluid or consolidation of the lung by pressure of the elevated diaphragm on the affected side, (3) when there is an air bubble beneath the

diaphragm and above the liver, and (4) when the patient has an unexplained fever following upper abdominal surgery.

Respiratory complications such as pleurisy with effusion, pneumonia, and atelectasis may be found by physical signs or by the x-ray film.

Wound rupture may be partial or complete. At times the patient may feel something give way during a coughing or vomiting spell. This may be the origin of a ventral hernia. Immediate closure of the completely disrupted wound is most satisfactory. Adhesive strapping over sterile gauze is a very unsatisfactory makeshift.

Dehydration, hypochloremia, sodium chloride retention with edema, and embarrassment of the circulation from overloading are complications incidental to postoperative fluid balance. Hiccup is caused by irritation of the diaphragm or of a reflex arc involving the phrenic nerves. The cause should be sought according to the classification of Mayo. Prevention of distention by the early use of *morphine*, *intestinal suction*, and *gastric lavage* with *sodium-bicarbonate solution* may be helpful. *Narcotics* and *sedatives*, and *carbon dioxide* and *oxygen inhalations* for not more than 15 minutes at a time usually are effective. If the hiccup persists more than 7 days, interruption of the phrenic nerve pathway may be necessary. Cervical infiltration of the phrenic nerve with 2 per cent novocaine should be done on 1 or both sides with the patient under the fluoroscope, and the effect on the excursions of the diaphragm should be noted.

Injury to the common duct occurs most commonly because the duct is clamped during an attempt to control a bleeding cystic artery or because the common duct is pulled up with the cystic duct and is tied or cut off. Obstructive

jaundice appearing within a few days after cholecystectomy, especially if not accompanied by pain, usually indicates injury to the common or hepatic ducts and in the authors' opinion demands an *immediate secondary operation* for correction.

Drainage of bile into the peritoneal cavity is dangerous because of the production of bile peritonitis. Distention, ileus, nausea, vomiting, and death may follow. This may result from too early removal or slipping of the T-tube in the common duct. If the patient's condition permits, *reoperation with reinsertion of the tube* is indicated.

Stones remaining in the common duct may be demonstrated by lipiodol injections through the T-tube. The use of *ether* to "dissolve" the stone has been reported.

Hemorrhage in a case of gall-bladder disease without jaundice usually indicates bleeding from an uncontrolled cystic artery stump or from damaged liver tissue, or oozing from a plexus of veins overlying the common duct. Serious hemorrhage warrants *transfusions* and *reoperation* to control the hemorrhage. In the jaundiced patient preoperative preparation should be adequate with *glucose*, *vitosterol*, and *transfusions*. Glucose administered postoperatively and repeated transfusions are found to be of value.

"Liver failure" is a blanket term that in the absence of a postmortem examination covers a variety of conditions associated with serious depletion of the vital forces. In the patient gravely ill with cardiovascular and renal disease the prospect of "liver failure" is great and efforts should be made to improve these organs.

Pancreatic and biliary fistula if persistent are serious and require *reconstructive surgery*.

Injuries to the Extrahepatic Bile Duct—Rarely are injuries to any structure attended by such distressing complications as are injuries to the extrahepatic bile ducts. H. K. Gray⁶⁴ states that in a high percentage of cases the process of healing results in scar formation, which, by contraction, encroaches

Etiology—Injuries to the extrahepatic bile ducts occur most frequently during the course of cholecystectomy. Such a catastrophe can be avoided in the majority of instances through the exercise of proper care in isolating and visualizing the distal portion of the common hepatic bile duct and the proximal

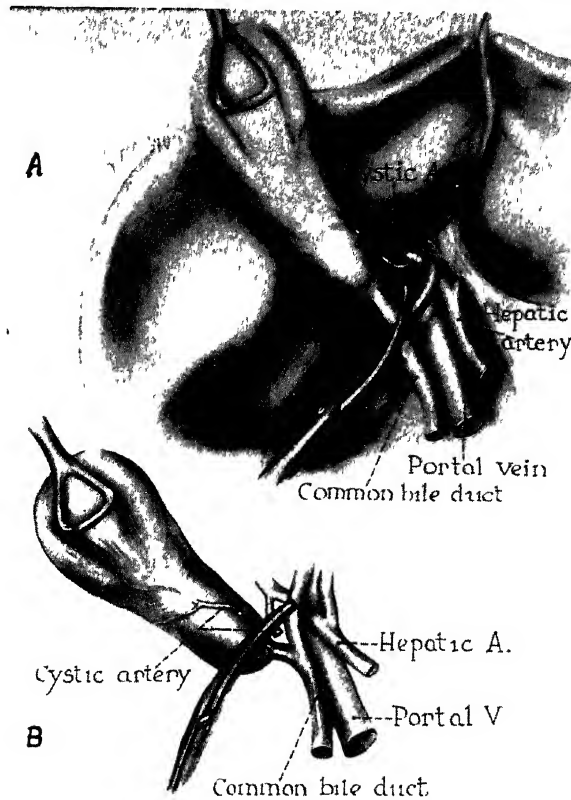


Fig 36—*A*, when traction is made on the gall-bladder, the common duct may be angulated and traumatized in placing a hemostat from the lower end of the cystic duct *B*, the right hepatic duct may be injured by blind instrumentation in attempting to control bleeding from the cystic artery. (Am Jour. Surg., 40 218, Apr, 1938)

upon the lumen of the bile duct and thus interferes with hepatic function directly by mechanical obstruction and indirectly by parenchymal damage. In such instances, whether or not there is an associated biliary fistula, it becomes necessary to establish adequate biliary flow by surgical means. Perhaps in no other field of abdominal surgery is there greater need for sound surgical judgment and technical skill

portion of the common bile duct before sectioning the cystic duct. Because of the many anatomic variations which occur in this region, and because the tissues not infrequently are greatly distorted by inflammatory reaction, damage to the extrahepatic ducts may be imposed even by the most expert operator

Contrary to the impression which is held generally, injury occurs more frequently when the operative procedure is

relatively simple than when exposure is made difficult by a high-lying liver, or by a severe degree of inflammation in the gall-bladder or in the extracholecystic or extracholedochal tissues. When adequate exposure is accomplished without

difficulty, all of the tissues are relatively mobile and the common bile duct may become angulated by traction on the gall-bladder. Unless great care is exercised under such circumstances, a small portion of the wall of the common bile duct

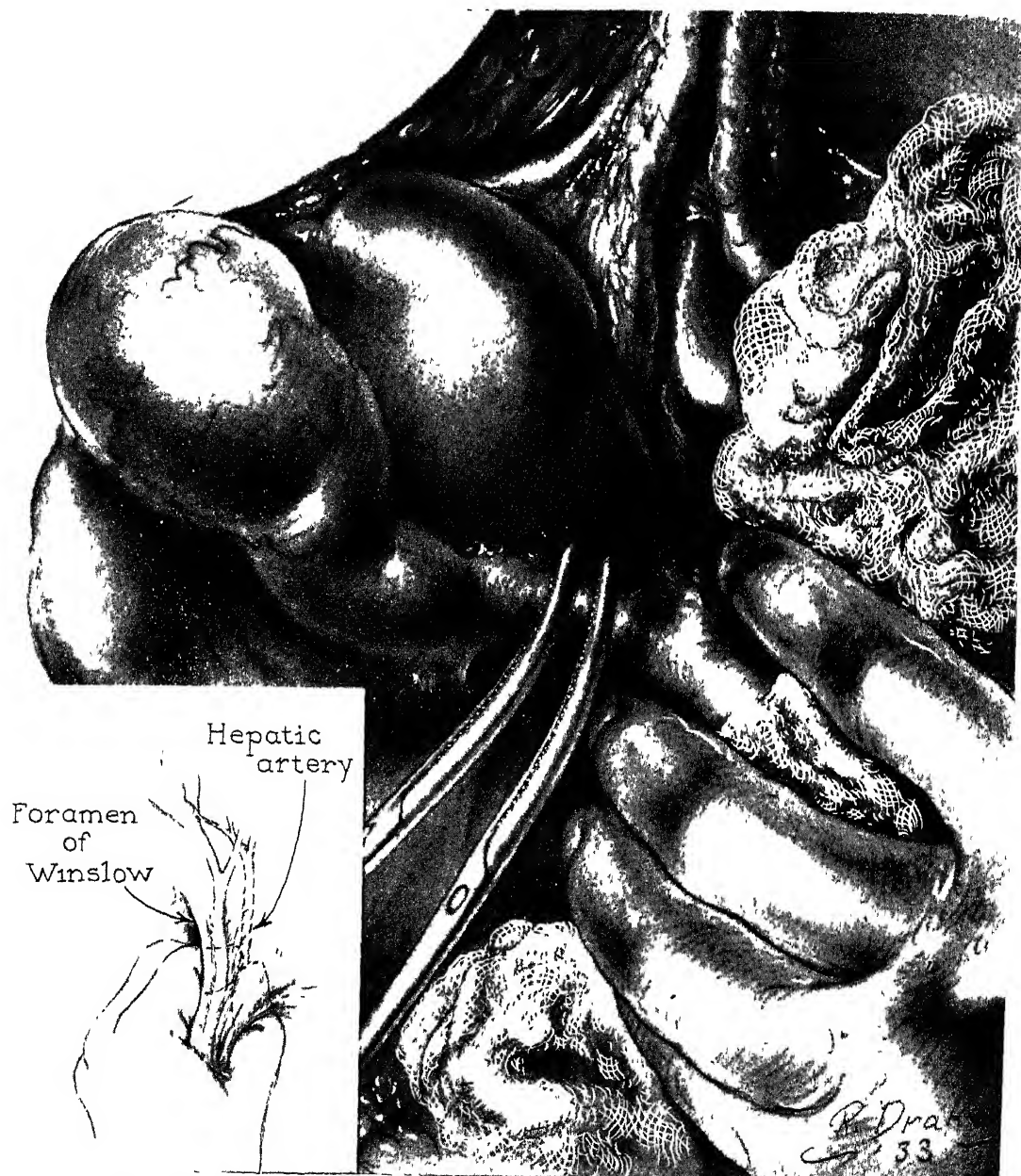


Fig 37—In order to obtain satisfactory exposure, the stomach has been gently packed mesially and the hepatic flexure of the colon mesially and caudally. The left hand of the first assistant is utilized in such a manner as to straddle the lateral border of the duodenohepatic ligament with the index and third fingers. Insert, the index and third fingers have been inserted through the foramen of Winslow and pressure applied to the hepatic artery by these 2 fingers and the thumb in order to control bleeding from the cystic artery (Am J Surg, 40: 219, Apr, 1938)

at the apex of the angulated area may be included in the clamp that has been placed on the distal end of the cystic duct (Fig. 36) Further encroachment upon the lumen of the duct will result when this area is ligated. The fact has been stressed repeatedly that it is not

the common bile duct. In this situation, and if there is any doubt as to the presence of a retained stone or stones in the distal portion of the cystic duct, it is safer to section the duct proximal to the suspected area and to explore thoroughly the distal segment before ligation.

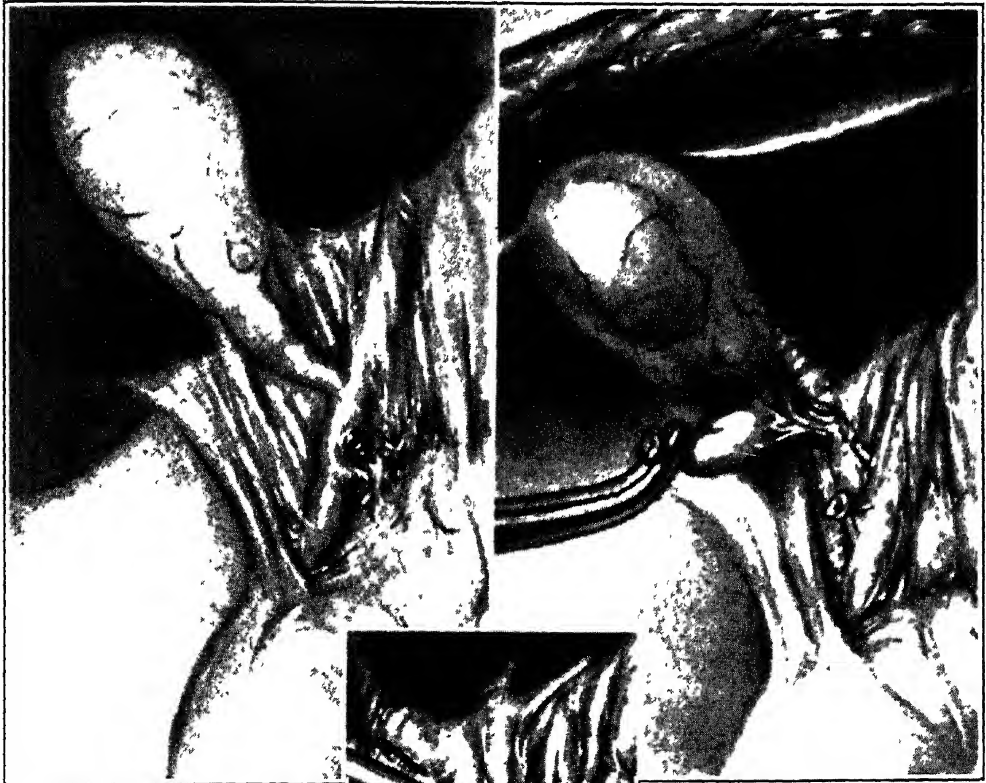


Fig 38—The method by which a stone ulcerating through the common duct can produce a stricture

Insert shows how a clamp which catches the bleeding end of the cystic or right hepatic artery can also catch the hepatic duct and cause stricture (Annals of Surgery, 105 5, (May) 1937)

Fig 39—Showing how when the cystic duct is clamped and cut before the cystic artery is clamped and cut traction is upon the artery and can tear that structure, causing annoying hemorrhage (Annals of Surgery, 105 5, (May) 1937)

necessary to remove the entire cystic duct during cholecystectomy. Not infrequently a stone may become impacted in the cystic duct so close to the common duct that it is impossible from a technical standpoint to divide the cystic duct distal to the stone without injuring

Results—In an attempt to discuss injuries to the extrahepatic bile ducts, it has been difficult to approach the subject in a different manner. Consideration has been given to the etiology of benign stricture and the pathologic physiology of the liver in order to em-

phasize the serious consequences of injury to the extrahepatic bile ducts. The distressing features of this condition may be emphasized further when it is considered that of 228 patients with stricture of the extrahepatic bile ducts who were operated on at the Mayo Clinic in

patients in whom strictures occurred had been operated on previously for disease of the biliary tract. Although operative trauma may have no relation to the production of the stricture in some instances, it is certain that the incidence of stricture of the extrahepatic ducts can be

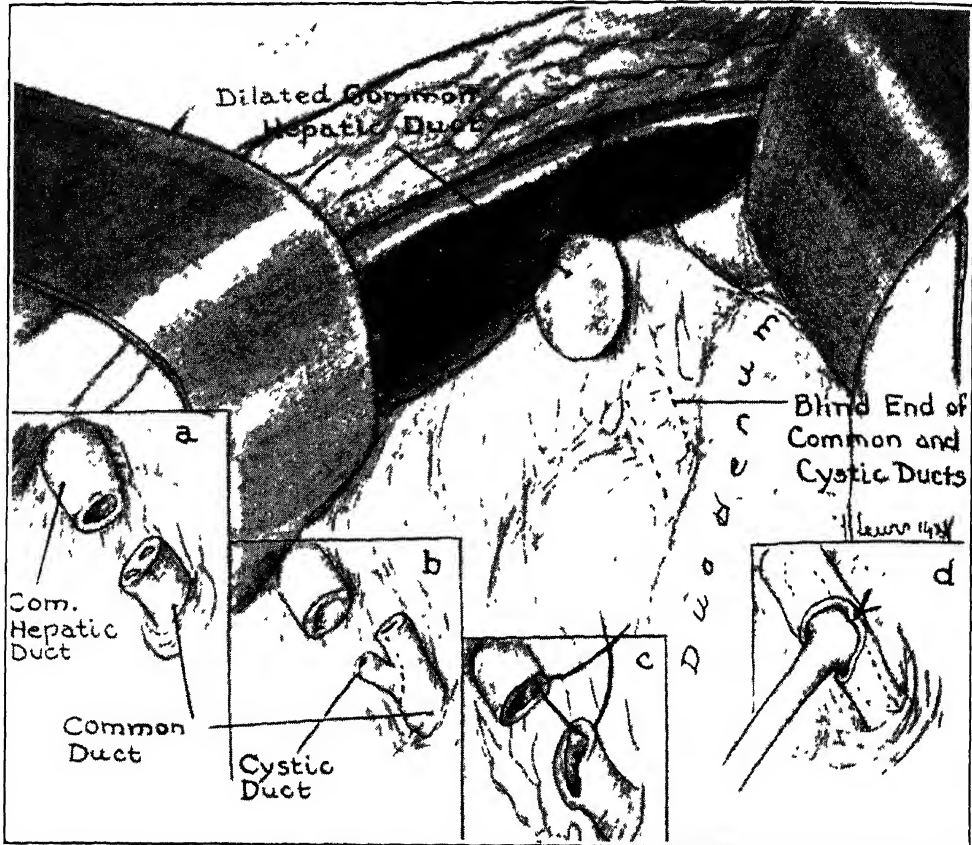


Fig 40—End-to-end anastomosis of common duct for complete division of duct following cholecystectomy (Annals of Surgery, 105 5, (May) 1937)

the 20-year period from 1917 to 1936, inclusive, 175 (76.7 per cent) were women. Seventy-three (32 per cent) of the total number of patients with stricture were in the fourth decade, and 64 (28.1 per cent) in the third decade of life. Eighteen (7.9 per cent) were less than 30 years of age. In other words, of 10 patients with stricture of the extrahepatic bile ducts, 7 will be less than 50 years of age. Practically all of the

reduced if meticulous care is exercised in performing any operation on the biliary tract.

Treatment—In operating upon the common and hepatic duct strictures, F. H. Lahey⁶⁵ attempts to select the operative procedure which offers the best chance of draining the bile into the intestinal tract at the first operation, as secondary operations after failures upon patients with these lesions are much

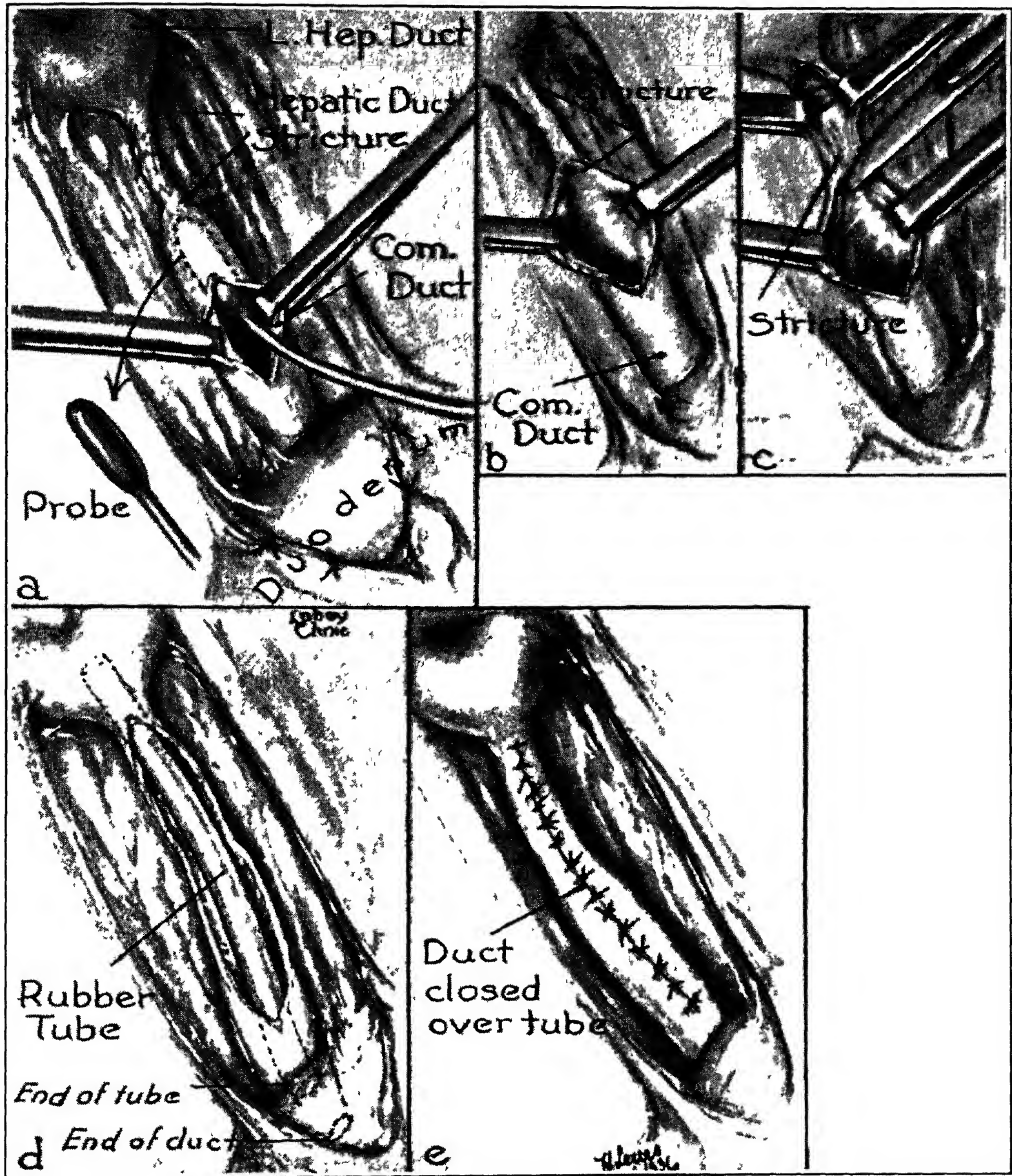


Fig 41—Stricture of hepatic duct caused at operation by clamping of the duct in an attempt to control hemorrhage from hepatic artery. Illustrations demonstrate method of treatment of this stricture. (Annals of Surgery, 105: 5, (May) 1937.)

more complicated and much less likely to be successful.

Repairs fashioned after the Heineke-Mikulicz plan in long strictures of the common or hepatic ducts are doomed to failure since there will be too much tension on the sutures in the reconstructed duct. In such cases, anastomosis of the end of the hepatic duct with

common and hepatic ducts will be followed by separation unless there is a good deal of slack in both ends of the ducts and they come together easily. If they do not, it is much better to anastomose the end of the hepatic duct with the duodenum.

When the hepatic duct has been cut previously, careful inspection should be

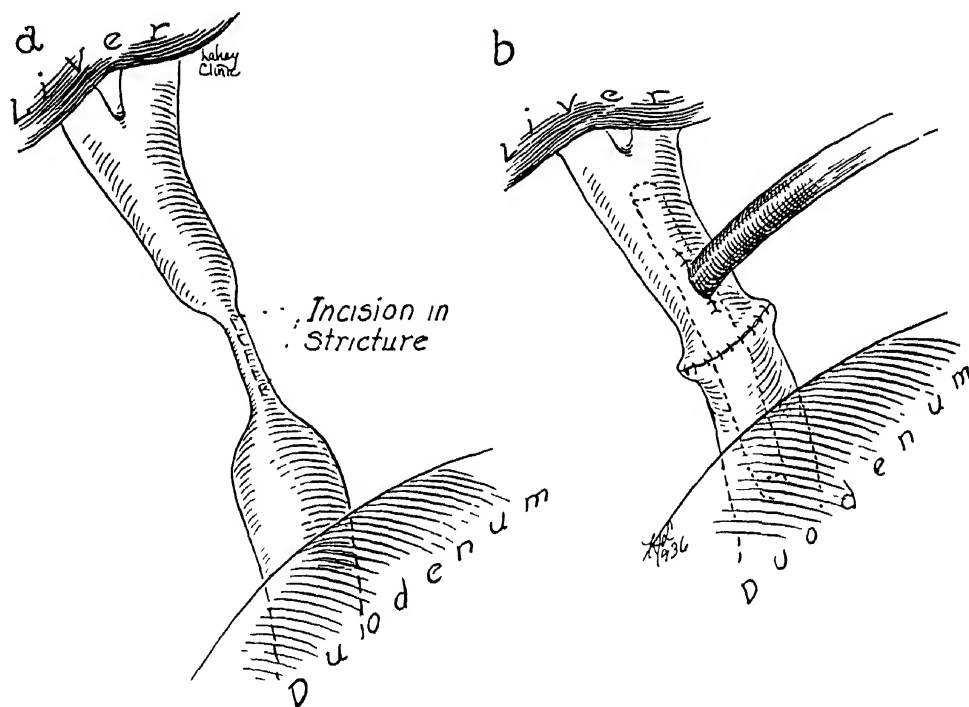


Fig. 42—Longitudinal incision of common duct stricture and closure about T-tube. Note position of upright limb of T-tube in relation to line of closure of stricture. (Annals of Surgery, 105: 5, (May) 1937.)

the duodenum will be a much more satisfactory procedure.

If a strictured duct is to be repaired by the Heineke-Mikulicz plan of plastic upon it, the T-tube is best inserted through a separate incision in the duct above the stricture, the lower limb of the tube passing through the incised stricture as in Case 6 and the plastic performed over this portion of the tube. This permits withdrawal of the T-tube without injury to the line of the anastomosis. End-to-end anastomosis of the

made of the amount of hepatic duct available for suture to the duodenum and a decision made as to whether or not a sufficient amount of duct projects from the liver bed so that a safe anastomosis can be effected. That is, in the author's hands, made easier by the employment of interrupted sutures.

When a rubber tube must be implanted as a substitute for a destroyed duct so that it projects into the duodenum, it is less likely to be successful than when it can rest in the hepatic duct

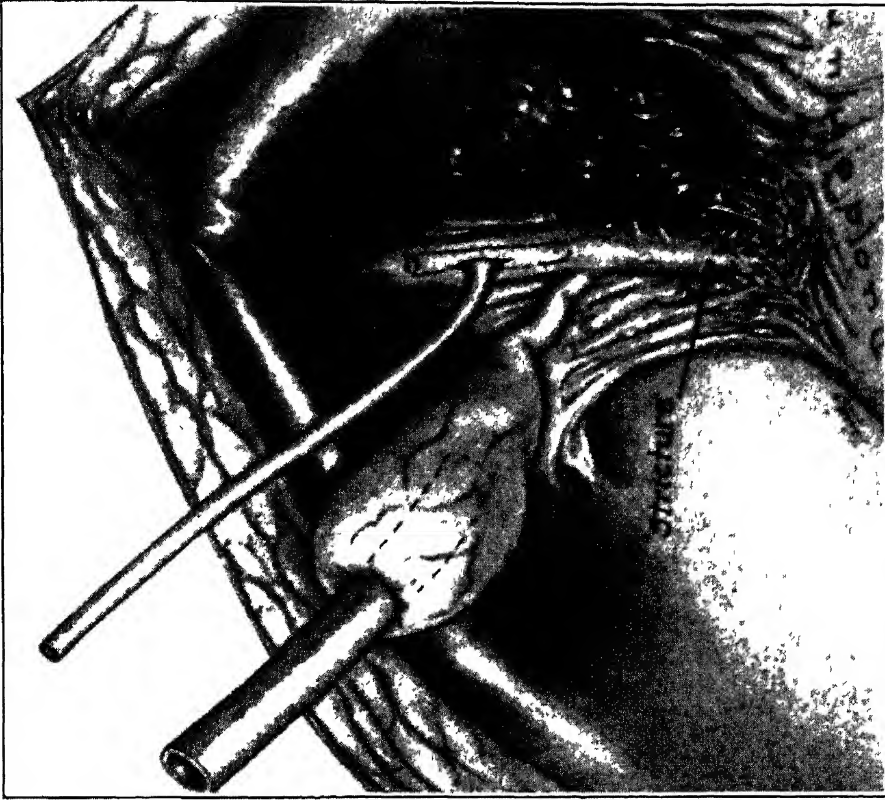


Fig 44—Drainage of hepatic duct and gall-bladder primary to cholecystgastrostomy (Annals of Surgery, 105 5, (May) 1937)

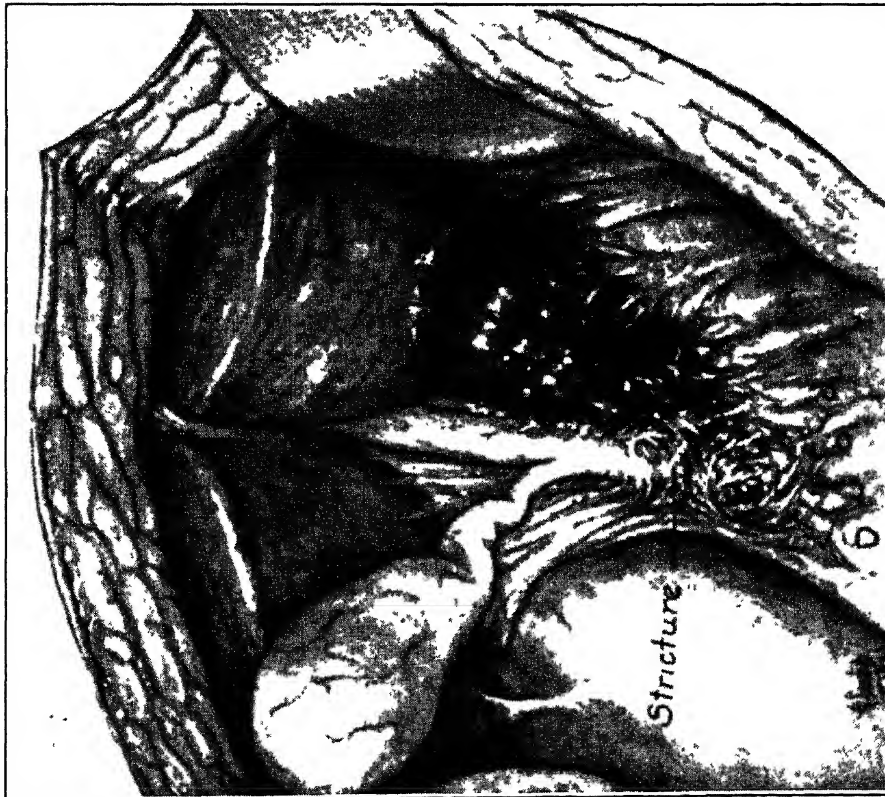


Fig 43—Stricture of common duct following auto accident with intra-abdominal injuries (Annals of Surgery, 105 5, (May) 1937)

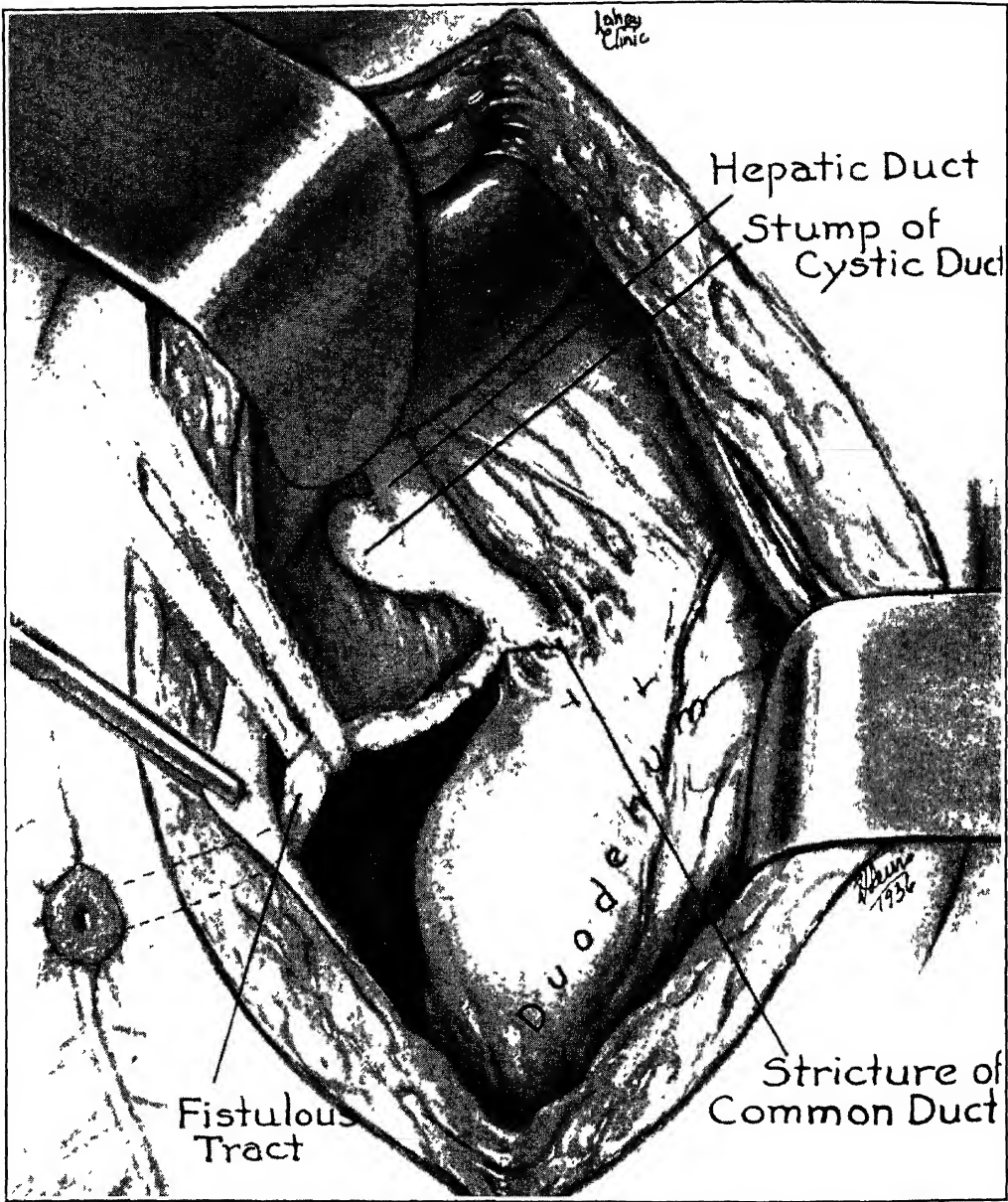


Fig 45—Stricture of common duct caused by adhesions just above the duodenum and fistulous tract of external biliary sinus (Annals of Surgery, 105 5, (May) 1937)

and common duct to bridge a defect and not pass to or through the sphincter of Oddi.

The implantation of the end of a cut duct with a section of catheter tied in it to prevent its constriction by the purse-string suture which holds it in the duodenum will at times, Lahey believes,

tion before the cystic duct is cut in cholecystectomy will prevent most of the cystic or hepatic artery hemorrhages in cholecystectomy, which in turn will prevent duct injury and the production of duct strictures.

Finally, there must be no more distressing situation in surgery than that

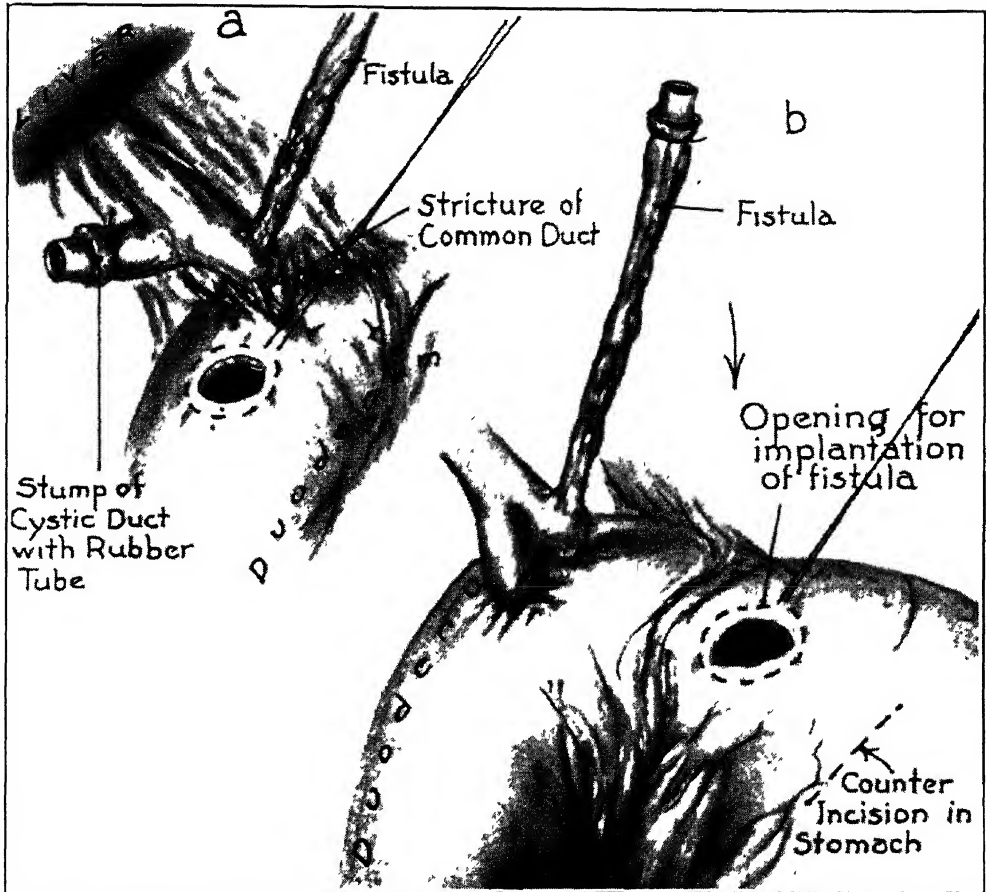


Fig. 46—Implantation of stump of cystic duct into duodenum and opening in stomach for implantation of external biliary sinus. (Annals of Surgery 105: 5 (May) 1937.)

be safer than direct suture between the end of the duct and the duodenum.

The production of an external biliary fistula and its implantation, while an undesirable operation and one in which many failures and recurrence of stricturing will occur, will occasionally need to be practiced as a last resort.

Careful preliminary isolation of the cystic artery and its clamping and liga-

associated with the production of a hepatic or common duct stricture. There is no result in surgery which is more gratifying than the successful operative relief of this condition and there is no place in surgery where surgical judgment and technical skill can better be exhibited than in the operative management of strictures of the common and hepatic ducts.

BILIARY TRACT

Cholangiography

Cholangiography is the roentgenographic visualization of a part or the entire intrahepatic and extrahepatic biliary tract after injection of a contrast substance at the operating table or postoperatively through a drainage tube or fistula. In 1934, Best and Hicken began

a means of diagnosing these elusive stones and thus avoiding incision into the common duct unless it was absolutely necessary. In their experience, immediate cholangiography has determined the presence of pathology when previous methods have failed. In view of the surgeon's fallibility in determining the status of the common duct by the usual methods, the question immediately



Fig 47



Fig 48



Fig 49

Fig 47—A normal immediate cholangiogram taken at the operating table. Fig 48—Immediate cholangiogram depicting a small stone at the lower end of the common duct which had not been palpable. Fig 49—An immediate cholangiogram depicting a rather large stone movable within the dilated common duct. (Surg., Gynec. & Obst., 66: 126, (Feb.) 1938.)

to make routine studies of the biliary tract in all cases of postoperative drainage, and instituted cholangiograms at the operating table. R. R. Best⁶⁶ applied the term "immediate cholangiography" to the latter method of visualization and "delayed cholangiography" to those studies made postoperatively.

Best and Hicken, after several months' experience with postoperative cholangiography and after having demonstrated stones remaining in common ducts which had been thoroughly explored at operation, believed there was good reason for attempting immediate cholangiography as

arises as to whether or not cholangiography should be a routine procedure in biliary-tract surgery. The experience of others will more correctly evaluate it, as well as improve the technic. Best and Hicken set up their equipment for taking an immediate cholangiogram in almost every case and take 1 in 75 per cent of the cases which present no definite indication for opening the common duct. They open the duct only if there is a history of jaundice, if there are palpable stones, if the duct is enlarged and thickened, or if the head of the pancreas is thickened. Immediate cholan-

giograms have obviated the necessity of incising the duct when the history of jaundice is vague, or when the presence of stones is questionable, unless definite evidence of pathology appears on the film.

Technic—After the common duct has been identified with a 23-gauge needle

angle of the wound are removed as they may overshadow the common duct; a large sterile sheet is thrown over the entire operative field; the mobile x-ray unit is brought into place; and the cholangiogram is taken, developed, and interpreted before removal of the gall bladder is completed.



Fig 50



Fig 51



Fig 52

Fig 50—Sixty cc of lipiodine were injected into the external biliary fistula. The gall-bladder appeared normal. The proximal three-quarters of the cystic duct was visualized but exhibited some peculiar configurations that were taken to be the spiral valves of Heister. The distal one-quarter of the duct was occluded. An organized bile-stained mucous plug was found to obstruct the cystic duct and it protruded into the neck of the gall-bladder. Bile could enter the gall-bladder but the ball valve action of the clot prevented its return through the cystic duct, hence the external fistula (Surg. Gynec and Obst 66 126 (Feb) 1938)

Fig 51—Delayed cholangiogram showing lower end of the common duct. Although the duct was dilated, the stone could not be palpated because the head of the pancreas was greatly thickened (Surg. Gynec and Obst 66 126 (Feb) 1938)

Fig 52—Multiple stones within the common duct, none of which were palpated at operation. Scooping, irrigation, and suction did not identify them. Recovery of the stones from the stool substantiated the cholangiographic findings (Surg. Gynec and Obst 66 126 (Feb) 1938)

on a 10 cc syringe, from 10 to 20 cc of a 48 per cent solution of hippuran is injected through a 22-gauge, short-beveled needle, $1\frac{1}{4}$ in long; a bead $\frac{1}{8}$ in. from the needle point lends security in locating the end of the needle so that it does not pierce the posterior wall of the common duct. After the needle is withdrawn, the Allis clamps are released and the puncture wound is gently sponged. The towel clips at the upper

Best and Hicken strongly advise cholangiographic studies in every case with T-tube or catheter drainage and in every fistula. Their earliest paper dealt with the value of cholangiography in depicting the presence of spasm at the lower end of the common duct, spastic biliary dyssynergia.

The first step in making a delayed cholangiogram is to withdraw, if possible, any residual bile from the biliary tract

through the tube, catheter, or fistula with a sterile syringe. Then from 10 to 25 cc. of warm 48 per cent hippuran solution is slowly injected. If the pain becomes very marked, it means the tract is under pressure and is probably filled. If an iodized oil is used, it is warmed



Fig. 53—Note the marked dilatation of the bile ducts. An obstruction near the ampulla has prevented the lipiodine from entering the duodenum. Radiograms made 3 hours later indicated the pseudo-obstruction had disappeared for the lipiodine was then in the jejunum. A spasm of the choledochal sphincter followed by a relaxation offers a probable explanation for this observation. (Unfortunately the 3 hour plate was destroyed.) (Surg., Gynec. and Obst. 66:126 (Feb.) 1938.)

and diluted about one-third with sterile warm olive oil. Thorotrast should also be slightly warmed. Delayed cholangiograms can usually be taken after the seventh or eighth postoperative day, and can be repeated as necessary. The plate can be taken with the patient in his bed if he cannot be moved, or on a radiographic table if he is ambulatory.

Interpretation—The presence of stones is most admirably shown by injection of radiopaque solutions into the biliary tract, and this fact accounts for most of the reports on this subject. Stones have been depicted singly or in

numbers along the intrahepatic and extrahepatic ducts. A collection of air in the duct will occasionally appear as a stone but recheck of the cholangiogram will establish its identity. Since iodized oil does not mix with bile, an occasional unfilled area may simulate a stone, but recheck or the use of a nonoily radiopaque medium will clarify the situation. Collections of inspissated bile, debris, or blood clots are usually quite irregular in shape and tend to shift their position. Stones as a rule have a sharper outline.

Strictures are apt to occur near or slightly below the junction of the cystic and common ducts and more frequently are the result of postoperative contractures. Adhesions not infrequently distort the outline or make it appear that a contracture is present. However, if there is no dilatation above the level of the apparent narrowing, it is probably not pathological. Buckling of the drainage tube may also give the appearance of a contracture. Patency of the common duct should be definitely established before the tube or the catheter is removed.

Cholangiectasis and dilatation of the hepatic ducts may be caused by a previous or existing obstruction or by infection. In gross dilatation a recheck should always be made to disprove the presence of an obstructing agent. The return of the dilated biliary tree to somewhere near its normal size is a means of determining when to remove the remaining drainage tube in the common duct.

A critical evaluation of cholangiography is made by C. G. Mixer and L. Hermanson.⁶⁷ The authors point out the frequency with which choledochostomy is performed with negative findings. This frequency may be decreased by the use of cholangiography at the operating table in those cases in which doubt exists as to the necessity for this exploration.

The injection of hippuran through the cystic duct is preferred to puncture of the common duct to prevent bile leakage which necessitates drainage and to prevent obscuration of the picture by spilled contrast media. A second film is recommended after choledochostomy to determine the results of the operative procedure.

One hundred and five cases are reported; 39 of these showed normal cholangiograms and the ducts were not opened. Only 2 of the patients have had symptoms subsequently suggestive of stones in the common duct. For this reason the authors believe that the cholangiogram is not to be relied upon in the presence of small stones or bile sand in the common duct.

In 21 patients cholangiography was done before and after the common duct was opened. Two cases showed a block at the ampulla believed to be due to spasm, since no organic pathology could be found. Eight cases showed a normal picture before the duct was opened, 7 of these pictures were proved correct, while 1 patient had stones in the common duct. Thus in this series 93.6 per cent of the findings were correct. Of the 13 patients remaining in this group, all were diagnosed from cholangiograms to have obstruction. Eleven of the diagnoses were correct. The 2 errors were substantiated by later cholangiography. In 1 case there was no stone and in the other the stone was not found until a later operation.

Fourteen patients had cholangiography only after exploration of the common duct. Nine of these had stones in the common duct and after removal of the stones the cholangiograms were normal. The subsequent history of these patients has indicated the presence of more stones in the common duct in only 1. The remaining 5 patients in this group had

no stones in the common duct on exploration; 4 of them had correspondingly normal cholangiograms. The fifth showed a dilated duct, but patent ampulla, in the cholangiogram. A subsequent choledochoduodenostomy was performed for the relief of the symptoms. The check-up



Fig. 54—This shows the marked dilatation of the biliary tree that occurs with carcinoma of the head of the pancreas as depicted by cholangiography. (*Surg., Gynec. and Obst.* 66: 126 (Feb.) 1938.)

cholangiograms were thus correct in 92.8 per cent of the cases.

Postoperative cholangiography is useful in the determination of when the drainage tube should be withdrawn and was proved correct in 94.7 per cent of 76 cases.

The authors state that cholangiography is unnecessary in those cases in which the history or examination of the ducts at operation is sufficient to indicate choledochostomy, but that as a check-up following such exploration it is invaluable.

Jaundice

Preparation of the Jaundiced Patient for Operation—The preparation of the jaundiced patient includes all of the precautionary and rehabilitative

the liver and resultant liver anoxemia, may be overcome in most cases by the use of ephedrine preoperatively.

Postoperative Treatment—During the postoperative period, the problem of liver insufficiency may persist in even greater degree because of trauma and anesthesia and treatment during this period must be designed to meet this. The glucose intake must be kept up and, as the patient seldom takes much by mouth during the initial phase of the postoperative period, a *continuous venoclysis of a glucose solution* should be given. A *high carbohydrate diet* should be given as soon as possible.

The problem of keeping up the oxygen supply of the liver parenchyma presents several important aspects. It is of prime importance in this regard to maintain the respiratory exchange and to prevent atelectasis or other pulmonary complications. To this end it is the rule to insist on hourly change in position and hourly deep breathing exercises re-enforced, if co-operation is not forthcoming, by inhalations of oxygen (90 per cent) and carbon dioxide (10 per cent). Any tendency for mucus to collect in the bronchial tree is combated with expectorants, steam inhalations, and regular encouragement of the patient to cough. To reduce incisional pain during coughing, a tight binder is applied and often an attendant supports the patient's abdomen with his hands during the attempts to cough up the mucus. Atropine is not employed as it is believed it makes the bronchial secretions thicker and more likely to occlude the bronchi.

Incision—A transverse or subcostal incision is used routinely which seems to permit abdominal respiration sooner than the right rectus incisions. On the basis of the statistics collected by Ravdin and Kern, every reasonable endeavor is made to complete the operation in as short a

time as possible. In occasional instances patients have been given oxygen therapy after operation with the hope that higher oxygen tension would lead to better oxygenation of the liver cells.

Anemia should be corrected preoperatively and if much blood loss is sustained at operation, it should be promptly repaid by *transfusion*. It is of particular importance to prevent any depletion of blood volume as the resultant circulatory adjustment may seriously lower the arterial oxygen tension and blood flow to the liver may be seriously reduced.

The importance of biliary decompression already has been referred to and is discussed fully by Ravdin and Frazier. While admitting the theoretical advantages of clamping the common duct before it is opened as recommended by Culligan, the practical disadvantages of this maneuver have yet to be overcome. After the tube is sutured into the common duct, decompression should be carried out by a continuous method rather than by the intermittent method of Culligan.

The incidence of "pancreatic asthenia" became extremely low with the introduction of the practice of refeeding bile to patients with prolonged excessive bile drainage. By increasing the pressure in the drainage tract with a decompression apparatus, the excess bile can usually be forced into the duodenum, thus obviating the cumbersome method of refeeding bile through a stomach tube.

"Liver shock," like "pancreatic asthenia," has become a rare complication. As a condition similar to "liver shock" regularly appears in dogs when the hepatic artery is ligated, it seems possible that this condition is related to liver anoxemia. It would seem possible that an occasional instance of human liver shock might be due to unintentional ligation of a hepatic artery or to throm-

basis of this vessel during convalescence. This condition is included by Heyd and by Boyce and McFetridge in their discussions of so-called liver death. It is nearly always encountered in the group of patients who die within 48 hours with high fever.

Types of Jaundice Found in Infants and Children — Infants with jaundice must be carefully studied before any surgical procedure of the biliary tract is to be considered. G. C. Penberthy and C. D. Benson⁷⁰ state that the probable cause of the jaundice must be investigated. In the jaundice associated with hemolytic sepsis, the liver is usually enlarged, the stool is not acholic, and there is usually no bile in the urine. The icteric index is high and the jaundice is usually not progressive in type. The great majority of cases of jaundice in the newborn are of this type, and are secondary to a navel infection. Congenital lues with jaundice can easily be differentiated by the blood Wassermann or Kahn reaction of the mother and child and a roentgenologic examination of the skeletal system. Icterus neonatorum is characterized by the fact that an infant with this type of jaundice is usually not ill. The jaundice makes its appearance in about 2 to 3 days after birth, and disappears during the second week of life. There is no enlargement of the liver, no bile in the urine, and the stools are not acholic.

Erythroblastosis fetalis is a condition which has not received proper recognition as a distinct cause of jaundice. There has been some interest in the last few years in this disease, which was formerly known as *familial icterus gravis neonatorum*. The obstetrician should be particularly interested, because he has the first opportunity to recognize this disease in its earliest phase. It is a macrocytic, hemolytic anemia attended

by an intense bilirubinemia and jaundice which develops within the first 24 hours after birth. The *familial feature* of this disease is an important factor in the diagnosis. Hematologic studies reveal a high percentage of nucleated erythrocytes, the majority of which are normoblasts. The spleen and liver are enlarged, and on section, these and other depots of reticuloendothelium reveal many areas of extramedullary hemopoiesis. In the cases which have recovered in the past, the great majority have been treated by multiple small transfusions, but the mortality has been high. Penberthy with Cooley in 1935 reported a successful splenectomy in the treatment of this disease. The patient was 36 hours old, the second child in a family, in which the first had died on the fourth day after birth and was reported to have had severe jaundice. Before operation the icteric index was 300. The splenectomy was performed under local anesthesia. Nine days postoperatively the icteric index was 5 and the skin had regained its normal color. The convalescence was uneventful with no need for blood transfusions. At this date, according to the follow-up record, the child is in good health.

In older children with a tendency to jaundice, careful clinical and laboratory investigations are imperative, as there are other causes for jaundice foreign to the biliary tract. Hemolytic icterus is the one condition that deserves scrutiny. It is in this condition that splenectomy has brought such startling results. The gallbladder should be explored at the time of splenectomy, as cholelithiasis is occasionally a concomitant finding. The authors have observed no recurrence of the jaundice after splenectomy for hemolytic icterus "hypersplenism."

Two-Stage Operations in Obstructive Jaundice—It is well known that

patients with obstructive jaundice are poor surgical risks. This is due to a multiplicity of factors, such as the altered condition of the blood, the loss of detoxifying power of the liver, and the biliary stasis which predisposes to infection. These patients are therefore prone to hemorrhage, intoxication, and infection in the course of any surgical intervention.

O. Uffreduzzi⁷¹ suggests that in any case in which surgery on the biliary tract is contemplated, the functional capacity of the liver should be ascertained as accurately as possible. He admits that often this cannot be done because of the many factors entering into play and because of the unreliability of our liver-function tests. In general it may be said that complete biliary obstruction is more apt to develop hepatic insufficiency than an icteric individual with a partial obstruction.

The author believes that in cases presenting an obstruction of the biliary tract it is not a good plan to remove the obstruction by a 1-stage operation. It is more rational to combat first the condition of increased pressure within the biliary tract and prevent the resulting harmful consequences. In these conditions, therefore, it is most urgent to re-establish the bile flow and to restore the normal pressure within the biliary tract by way of a fistula.

The bile should be allowed to flow to the exterior rather than to drain into the intestine because in the latter case toxic substances and bacteria will be reabsorbed into the system.

When the bile is allowed to drain to the exterior it is also possible to explore the biliary tract roentgenologically by the injection of lipiodol into the biliary fistula.

The author thus advises that the biliary operations be divided into 2 stages.

The most commonly used surgical methods are cholecystostomy, opening of the cystic duct, or drainage of the latter through the gall bladder. In some cases it may be necessary to perform a choledochotomy and to insert a Kehr tube for drainage, but no attempt should be made to extract any stones which have become fixed to the lower segment of the common duct.

The interval which should elapse between the first and the second operation varies from case to case. The general criteria for proceeding to the second operation are indications, such as disappearance of the icterus, improvement of the patient's general condition, gradual subsidence of the fever, and, especially, improvement of the functional capacity of the liver.

The second operation will depend upon the individual case. Among a total of 9 cases the author performed a choledochotomy at the site of the stone in 6, a transduodenal papillotomy was performed in 2 because the stone was wedged into the papilla, and a choledochoduodenostomy was done in 1 case because the stone was extremely friable. The author recommends that if the stone cannot be dislodged it may be advantageous to transform external drainage by means of a cholecystogastrotomy. With these methods he was able to obtain very satisfactory results in his series of treated cases.

LIVER

Solitary Nonparasitic Hepatic Cysts

According to I. Baumgarten⁷² about 100 cases of solitary nonparasitic hepatic cysts have been reported in the literature since 1864. The majority of the cysts are caused by retention in the bile ducts, due to congenital malforma-

tion or to local obstruction of small intrahepatic bile ducts. Most of them give no symptoms. If symptoms do occur, they are usually due to pressure on neighboring organs. Exact diagnosis is rarely made before operation or necropsy. The only effective therapy is surgical intervention, and the ideal operation is extirpation. The highest operative mortality occurs in cases in which puncture is done, the lowest is radical operations. In the case reported, in a woman aged 26, extirpation of the cyst was followed by recovery.

Primary Carcinoma of Liver

In 24,400 consecutive necropsies performed at Bellevue Hospital from 1906 to 1936, E. G. Gustafson⁷³ collected data on 62 cases of primary carcinoma of the liver. In selecting these cases the classification and diagnostic criteria suggested by Eggel were adhered to. The majority of these patients entered the hospital with complaints referable to the liver. In the usual case there were 2 or 3 major complaints. However patients with vague gastrointestinal symptoms, pain in the right upper quadrant (frequently simulating that of cholecystitis) and rapidly accumulating ascites comprise the largest group of cases. Loss of weight as a symptom has an apparently minor part, having been mentioned in only 5 cases. This may be explained on the basis of the counteracting gain of weight due to ascitic accumulation. Several patients sought medical attention because friends noticed their rapidly increasing girth. Edema, especially of the dependent sort, was complained of by only 5 patients, although it was found more frequently on physical examination. It usually appears late in cases of primary carcinoma of the liver and is of differential significance in patients with complaints referable to

cardiac decompensation. Fever as a chief complaint was present in only 2 cases. Hematemesis occurred only once, as did diarrhea. The former fact is of interest because of its higher incidence in uncomplicated cirrhosis of the liver. In primary carcinoma of the liver the course is much shorter from the onset of symptoms to death than is that of cirrhosis of the liver. Collateral circulation is not as well established as it is in cirrhosis of the liver. The average course from onset of symptoms to death was 3.2 months.

Diagnosis—The diagnosis will be made more often if its relative frequency is borne in mind. Each of the 62 cases fulfilled at least 4 of the following criteria. A male patient more than 35 years of age, a large palpable tumor mass in the right lobe of the liver; no primary tumor discoverable elsewhere; jaundice (usually mild), ascites and an otherwise unexplainable fever of mild degree, and in the majority of cases 5 or even all of them. The author believes that a history of either vague gastrointestinal nature of short duration or signs of portal obstruction in the form of rapidly accumulating ascites should be used as additional information. The history of rapidly accumulating ascites in primary carcinoma of the liver is in contradistinction to that of ascites due to other causes—cardiac failure, tuberculosis or carcinomatosis of the peritoneum. In ascites of cardiac origin, evidence of its cause is practically always available. In ascites of peritoneal origin due to carcinoma, tuberculosis or the like causal factors are likewise apt to present themselves. On the other hand, rapidly accumulating ascites may be due to thrombosis of the portal vein of variable origin. In this connection it is to be recalled that neoplastic thrombosis of the portal vein not infrequently occurs in associa-

tion with primary carcinoma of the liver

Treatment—Surgical possibilities in malignant tumors of the liver in children and adults are outlined by M. Fevre and G. Dassios.⁷⁴ The authors are of the opinion that the indications for surgery can be extended to certain primary or even secondary cancers of the liver and are not restricted merely to solitary adenomas with a tendency toward malignancy in that organ. Diffuse cancers of the liver, diagnosed in a late stage, are of course inoperable, but the authors hope to demonstrate in this article that partial resection of the liver for malignant tumors is not as dangerous an operation as has been supposed, and that it may give very encouraging results.

They report 3 cases illustrating the surgical problems presented by malignant tumors of the liver. The first patient was a girl, 11 years old, in whom a primary cancer of the liver was definitely circumscribed and a *partial resection* was done; 14 months later an operation for glandular recurrence was performed; the patient was well 3 years and 3 months after the first operation. The second patient was a boy 3 years of age; symptoms had been present but for a few months when *exploratory operation* was done, yet the tumor had invaded the liver diffusely and removal was evidently impossible. The tumor ruptured during operation, and the patient died a few hours later. In the case of the third patient, a girl, 9 years of age, the tumor ruptured and caused acute symptoms which necessitated operation. The rupture was sutured, the sutures being placed in normal hepatic tissue and holding firmly. The patient showed temporary improvement and gained in weight, but died in 5 months.

The authors have collected 58 cases of malignant tumor of the liver in which

some type of operation was done, including the 3 cases reported above. Twelve of these cases were solitary adenomas with a tendency toward malignancy; 36 were primary malignant tumors, and 10 were secondary malignant tumors. Among the 58 cases, resection was done in 48, an attempt at exeresis in 1, and an exploratory operation only in 9.

Solitary adenomas of the liver with a tendency toward malignancy are surrounded by connective tissue, but the latter is not a true capsule with a definite plane of cleavage between the normal liver tissue and the tumor. Primary cancers of the liver which are suitable for operation consist of a single mass or a central mass with small nodules around it, an area of sclerotic tissue around the tumor mass is a favorable sign, and indicates that the tumor is of slow development. Of the 36 cases of primary cancer of the liver in which operation was done, 11 occurred in children under 15 years of age, in 5 of these resection was done, in 1 an attempt at exeresis was abandoned during the operation, and in 5 exploratory operations only were performed. It is important to note the relative frequency of primary cancer of the liver in children. Among the 10 secondary malignant tumors of the liver, the primary growth was at a distance in 6 cases, in 4 cases it invaded the liver by direct extension. Even in these cases removal of the secondary tumor may improve the patient's condition and prolong life.

In the 10 cases in which exploratory operation was done, 4 with biopsy, there were 7 postoperative deaths. The reason for the deaths was that the operations were done in a late stage when the tumor was friable and hemorrhagic, and the patients were in poor condition. In considering the possibility of resection of a malignant tumor of the liver, the liver

should be carefully inspected and palpated, if there is a single mass without diffuse involvement, it should be removed, even if it is large. Hemorrhage is more easily arrested if complete removal of the tumor is done. Even in

up; 8 had recurrences; 3 are living and well 2 years or more after operation. In the 8 cases with recurrence, the recurrence developed less than a year and a half after operation in 6; but there was 1 recurrence as late as 3 years after

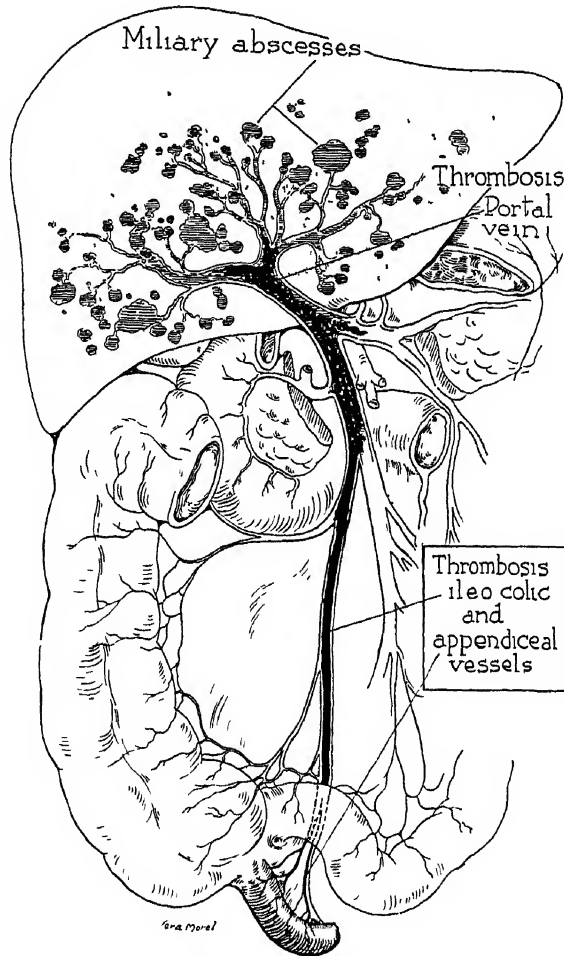


Fig. 56—Diagrammatic drawing illustrating pathogenesis of multiple abscess of liver following acute appendicitis. Pyothrombosis involves progressively the appendiceal veins in the meso-appendix, the ileocecal and ileocolic, the superior mesenteric, and finally the portal vein (American Journal of Surgery 40: 1 (Apr.) 1938)

partially encapsulated tumors, resection should be extended into normal hepatic tissue. Hemostasis may be obtained by the use of the electric cutting current, or by ligature.

In the 12 cases of adenoma with a tendency to malignancy in which resection was done, there were no postoperative deaths. One patient was not followed

operation. Among the 26 cases of primary malignant tumor in which resection was done, there were 4 deaths within 2 weeks after operation, 15 could be followed up. Of these, 7 showed recurrences, all within 1 year, 8 were living and well from 1 to 4 years after operation. Among the 10 cases of secondary tumor of the liver, in which

partial resection was done, there were no postoperative deaths. The ultimate results depended upon the nature of the primary tumor, but in most cases especially when the primary tumor was at a distance, the patient's condition was definitely improved. In 1 case in which the liver tumor was secondary to a goiter removed a year and a half previously, the patient was living and in good health

ary in New Orleans. Of this number, 139 (74.7 per cent) were amebic abscesses and 47 (25.2 per cent) were pyogenic. During this same period there were 540,776 total admissions to the Charity Hospital, among which there were 160 (0.029 per cent) abscesses of the liver, and 1152 patients diagnosed as having liver disease, of which 10.2 per cent were amebic abscesses and 3.6 per

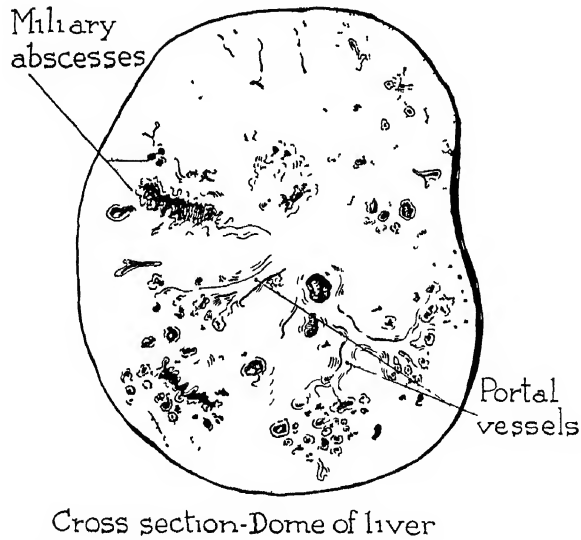


Fig. 57—Diagrammatic drawing of cross section through right lobe of liver in multiple pyogenic abscess following pylephlebitis. The grape-like grouping of abscesses clustered about terminal branches of portal vein is characteristic of this pathologic process. (American Journal of Surgery 40: 1 (Apr.) 1938.)

18 months after removal of the hepatic tumor. In another case in which the hepatic tumor was secondary to ovarian tumors, the patient was living and well 6 years after partial resection of liver.

Pyogenic Abscess of Liver

A review of 830 cases of pyogenic hepatic abscess collected from the world literature and a presentation of 47 additional cases is made by A. Ochsner, M. DeBakey and S. Murray.⁷⁵

Incidence—During the 10-year period, 1928-1937 inclusive, there were 186 cases of abscess of the liver admitted to Charity Hospital and Touro Infirmary

in New Orleans. Of this number, 139 (74.7 per cent) were amebic abscesses and 47 (25.2 per cent) were pyogenic. During this same period there were 540,776 total admissions to the Charity Hospital, among which there were 160 (0.029 per cent) abscesses of the liver, and 1152 patients diagnosed as having liver disease, of which 10.2 per cent were amebic abscesses and 3.6 per cent were pyogenic abscesses. The sex incidence of pyogenic hepatic abscess reveals a preponderance of occurrence in the male, 67.4 per cent in the collected series and 70.2 per cent in the authors'. This is probably explained by the fact that the etiologic agents occur more frequently in the male. The greatest age incidence is from the third to the fifth decades. There is no significant racial predisposition.

Pyogenic liver abscess is primarily a complication of an intra-abdominal suppurative process with the antecedent lesions in the portal area. Of these lesions, suppurative appendicitis is the most

frequent Appendicitis was the etiologic agent in 34.2 per cent of the collected cases and 10.6 per cent of the author's cases. This discrepancy is due to the fact that the majority of reports in the literature represented primarily the authors' interest in pylephlebitis and liver abscess as complications of appendicitis. Pyogenic liver abscess can be caused

cess are *B. coli*, streptococci, and staphylococci.

Pathology—Pyogenic hepatic abscess may be multiple or single and usually involves the right lobe. The abscesses were single in 28.8 per cent, multiple in 71.1 per cent, and involved the right lobe alone in 41.8 per cent of the collected cases. In the authors' 47 cases these



Fig. 58—Photograph of upper surface of liver from case of multiple pyogenic hepatic abscess. The small abscesses studding the surface of the liver may give the erroneous impression of multiple metastatic nodules from a distant neoplasm. (American Journal of Surgery 40:1 (Apr) 1938.)

also by direct extension from contiguous suppurative processes, trauma, and by transportation of microorganisms through the hepatic artery from distant foci. There is a relatively large group (59.5 per cent) of the authors' series termed "cryptogenic," idiopathic, or primary pyogenic hepatic abscess in which the antecedent lesion could not be determined.

Bacteriology—The most frequently found organisms in pyogenic hepatic ab-

incidences were 54.5 per cent, 45.4 per cent, and 68.1 per cent, respectively.

Symptoms—The principal symptoms and signs of pyogenic hepatic abscess are fever, pain and tenderness over the hepatic area, liver enlargement, chills, and jaundice. Characteristically, there is a leukocytosis with a proportionate increase in polymorphonuclear leukocytes. The characteristic roentgenologic changes are elevation and immobility of the diaphragm, usually the right. The diagnosis

was positive in 82.1 per cent of 28 cases in the authors' series in which roentgenologic studies were made

Prognosis—The prognosis in pyogenic hepatic abscess depends upon: (1) The multiplicity of the lesion; (2) the presence or absence of complications;

upon the mortality rate was 100 per cent in both series, in the cases in which operation was performed the mortality was 50.9 per cent in the collected series and 64.8 per cent in the authors' series.

The complications of pyogenic hepatic abscess are usually the result of rupture



Fig. 59—Cross section of liver in the chronic type of pyogenic hepatic abscess. An abscess cavity may be seen with a wall almost as thick as the diameter of the defect itself. Another cavity, more centrally located, is almost obliterated by fibroblastic proliferation. Still other areas reveal the characteristic extensive fibrous tissue formation in this type of pyogenic hepatic abscess. (American Journal of Surgery 40:1 (Apr) 1938.)

and (3) the type of drainage instituted. Whereas of the 24 cases in the authors' series with single abscess of the liver, 9 (37.5 per cent) died, of the 20 cases with multiple abscesses, 19 (95 per cent) died. The mortality rate was 90.9 per cent in those cases with complications and 36 per cent in the cases without complications. The total mortality rate was 79.6 per cent in the collected cases and 72.3 per cent in the authors' series. Whereas in those cases not operated

or direct extension into one of the adjacent viscera.

Treatment—The treatment of pyogenic hepatic abscess may be divided into (1) Prophylactic, and (2) surgical. Prophylaxis is particularly applicable to multiple hepatic abscesses which are preceded by appendicitis and pylephlebitis, because once the development has proceeded to the stage of multiple abscess formation, surgical therapy offers only the slightest hope. The treatment

of solitary pyogenic hepatic abscess consists of *incision* and *drainage*.

The employment of that type of drainage which completely avoids the slightest possibility of contamination of the peritoneal or pleural cavity is of paramount importance. The results obtained in the authors' series of cases clearly demonstrate this fact. Of the 22 cases in which the transperitoneal approach was employed for the institution of drainage, there were 16 deaths (72.7 per cent). The transpleural method of drainage was used in 9 cases with 6 deaths (66.6 per cent). In contrast to these high mortality rates is the 33.3 per cent mortality obtained in 6 cases in which the extra-serous approach was used.

Subphrenic Abscess

An analysis of 3583 cases of subphrenic abscess collected from the world literature and a presentation of 25 additional cases is made by A. Ochsner and M. DeBakey.⁷⁶

Incidence—The sex incidence of subphrenic abscess reveals a preponderance of occurrence in the male, which is probably due to a correspondingly greater incidence of the original lesion in the male. There is no significant racial predisposition. The greatest incidence with regard to age occurs in from the third to the fifth decades, inclusive.

Whereas the incidence of subphrenic abscess is not high, subphrenic infections occur much more frequently than is commonly supposed, but fortunately do not progress to suppuration.

Pathogenesis—Subphrenic abscess is primarily a complication of an intra-abdominal suppurative process. Over half of all subphrenic abscesses are the result of suppurative lesions of the appendix and perforative lesions of the stomach and duodenum.

The microorganisms most frequently obtained from subphrenic abscess are the colon bacillus, streptococcus, and staphylococcus.

The routes of extension of infection to the subphrenic spaces are rarely through vascular channels from neighboring or distant foci, but most frequently through intraperitoneal or extraperitoneal direct invasion or lymphatic drainage.

Diagnosis—The most frequently involved subphrenic space is the right posterior superior (33.7 per cent of the collected cases and 55.7 per cent of the authors').

Whereas the inaccessibility of the subphrenic region lends considerably to the difficulty in diagnosis, the frequent omission of and delay in the diagnosis are due in great measure to the failure to suspect its presence. The possibility of subphrenic infection always must be strongly suspected in every patient with continued pyrexia and leukocytosis who has had an antecedent suppurative intraperitoneal process and in whom no other accountable focus can be demonstrated. If these manifestations of infection persist instead of subsiding within a period of a few days to a week, and particularly if there is persistent localized tenderness over the involved portion or over the twelfth rib and roentgenological demonstration of elevation and immobility of the diaphragm, the diagnosis of subphrenic abscess is justified and exploratory operation warranted.

Complications—The most frequent complications of subphrenic abscess are intrathoracic inflammatory processes which are the direct result of delay in diagnosis and the institution of appropriate therapy. The gravity of these complications is shown by the fact that in the combined series of 75 cases the mortality of those cases with thoracic

complications was 50 per cent in contrast to 16.3 per cent in those cases with no thoracic complications.

Prognosis—Aside from the uncontrollable factors of virulence of the infection and resistance of the host, the 3 most important factors governing the prognosis are (1) The time elapsing between the development of the infection and the institution of therapy; (2) the presence of complications, and (3) the type of treatment employed

Treatment—Whereas the treatment of subphrenic infection is conservative, the treatment of subphrenic abscess is *surgical drainage*. Of 3038 cases, including 75 of the authors', there were 1096 cases treated nonoperatively with 985 (89.8 per cent) deaths as contrasted to 1942 cases treated by operation with 637 (32.8 per cent) deaths

The employment of that type of drainage which completely avoids the slightest possibility of contamination of the peritoneal or pleural cavities is of paramount importance. Of 932 collected cases, 394 had transpleural drainage with a mortality of 36.2 per cent, and 327 had transperitoneal drainage with a mortality of 35.1 per cent, while in the remaining 211 cases with extraserous drainage there was a mortality of 20.8 per cent. In the combined series the corresponding mortality rates were 50 per cent, 42.8 per cent, and 10.8 per cent

Whereas in the authors' previously reported 50 cases the operative mortality was 32 per cent, in the present group of 25 cases, it is 11.7 per cent. This material reduction in mortality is largely due to the greater percentage of employment of extraserous drainage procedures in the latter group.

In the 15 cases of the present group in which the type of drainage employed was extraserous, there was only 1 death (6.6 per cent).

The technic of the "retroperitoneal" operation is described. The results obtained by this method of drainage conspicuously show the advisability of its use and its advantages.

PANCREAS

Acute Pancreatitis

Cases of acute pancreatitis may be divided roughly into 2 types: the acute edematous, or interstitial type, and the acute hemorrhagic, or necrotic type. W. H. Cole⁷⁷ points out that it is possible that the acute edematous type is caused primarily by obstruction, while the acute necrotic type occurs as a result of tryptic digestion within the gland. The symptoms in the former type are milder and are never associated with shock. Analysis of the various clinical reports, in addition to the authors' observations, shows an increase in blood amylase in acute pancreatitis only. This is about as reliable in the acute interstitial forms as in the fulminating forms, except that a normal or low reading may be encountered more frequently in the latter group. There is a rise of blood amylase from its normal level of 90 to a level of 150 within a few hours, and in a day or two this may be as high as 1000 (Readings are expressed in terms of milligrams of sugar produced by the amylolytic action of 100 cc of serum on a given amount of starch.) The blood amylase level falls gradually until the normal threshold is reached within 2 or 3 days after the onset of the symptoms. It may return to normal many days before the symptoms subside, although often there will be a direct correlation between the return of blood amylase to normal and the subsidence of symptoms.

Urinary diastase determinations are of diagnostic value. However, there is a

great variation between blood amylase and urinary amylase. The test is positive in more than 50 per cent of the cases of pancreatic cysts. In carcinoma of the pancreas the test shows an increase in only a few cases. In chronic pancreatitis the test is negative.

A low blood-amylase level, in the light of recent work, is an indication of hepatic disease. The author observed such an instance in a patient with considerable destruction of the liver by cysts. A low amylase level may be found after a sudden elevation in the amount of amylase in the blood stream. The liver and pancreas cease to produce amylase during the period of elevation, but although the elevation disappears within a few days, the return to normal production takes from 8 to 20 days.

Gall-bladder disease is perhaps the most common etiological factor in the development of either of the types of acute pancreatitis. Prophylactic eradication of this source by cholecystectomy is justifiable, and depends upon the usual indications for gall-bladder surgery. There may be an additional indication even when attacks of cholecystitis are infrequent, if the presence of pancreatitis can be determined by clinical signs and from the amylase determination.

Treatment—It is generally agreed that the treatment of acute edematous pancreatitis should be *conservative*, to be followed later by *gall-bladder surgery* as indicated. Confusion still exists as to whether conservative treatment or immediate operation is the treatment of choice in acute pancreatic necrosis. A review of recent reports during the past few years indicates quite clearly that many surgeons are obtaining better results by treating this type of disease conservatively at first, and later by operating on the gall bladder or bile ducts as indicated. These reports and recent per-

sonal clinical experiences have led the author to modify his previous impression and favor conservative therapy. Conservative treatment as modified according to Rowland's recommendation should consist of:

1. Adequate *morphine* for pain.
2. Immediate determination of blood sugar and urinary or blood diastase.
3. Roentgenograms for the determination of gas under the diaphragm.
4. Nothing by mouth.
5. *Wangensteen suction* with removal of gastric and intestinal secretions to prevent stimulation of the pancreas.

In spite of the desire to maintain a conservative attitude, there will be numerous occasions when an emergency operation will be necessary, particularly when differentiation from a perforated viscus cannot be made. In general, immediate operation should be performed (1) When the diagnosis is uncertain; (2) when signs of peritonitis, including severe muscle spasm, are present, and (3) when an abscess is obviously present. If the conservative attitude is maintained operation should not be performed (1) When the diagnosis is certain, (2) when the evidence of vascular collapse is so severe that operation would be dangerous, and (3) as long as the inflammatory process appears to be confined to the retroperitoneal tissues about the pancreas. Recovery of the patient from epigastric distress is frequently slow even though the proper operative procedures upon the biliary tract have been carried out.

According to G. R. Dunlop and E. L. Hunt, the following sequence of events is logical in acute pancreatitis (1) Obstruction of the pancreatic ducts; (2) rupture of the duct-acinar system, due to back pressure; (3) escape of tryptic ferments; (4) necrosis of vessel walls,

and (5) hemorrhage into the interstitial tissue with necrosis of the gland.

The authors report the cases of 14 patients with a mortality of 14.3 per cent.

In these patients, the pain was less agonizing than that which is usual, and while generally referred across the upper abdomen, it was sometimes localized in either upper quadrant

forated appendix, ruptured duodenal ulcer, acute intestinal obstruction, rupture of a distended gall bladder, mesenteric thrombosis, ruptured ectopic pregnancy, and biliary-tract disease. In most cases showing elevated blood sugar and elevated urine amylase, blood sugar determinations and the Wohlgemuth test for urine amylase proved valuable.

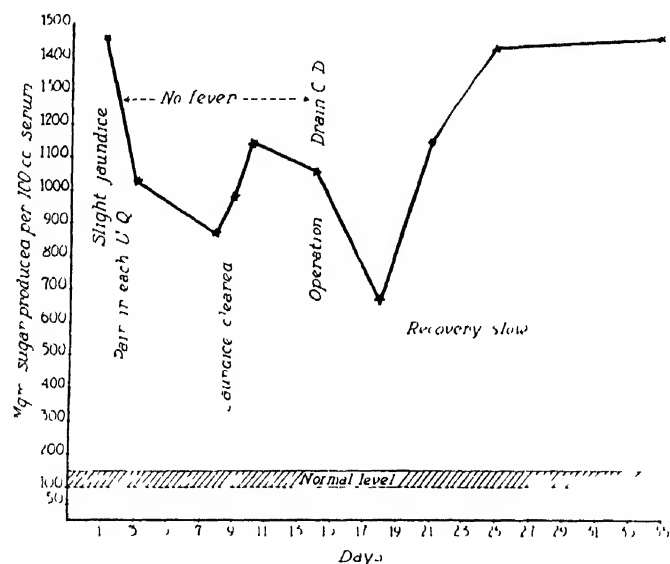


Fig. 60—The above graph represents the amount of retention of amylase in the serum of a patient with acute edematous pancreatitis, who developed an attack of epigastric pain 3 days before admission to the hospital. We delayed operation a few days expecting the amylase to drop to normal, as usually occurs. This elevation persisted for 2 weeks. Operation was finally performed in the hope that correction of the biliary disease would exert a curative or at least favorable influence on the pancreatic disease as it usually does. As will be noted on the chart, operation (cholecystectomy and choledochostomy for stone) was not followed by recession of the blood amylase over the period of 3 weeks illustrated on the chart. After 2 more weeks the amylase had dropped to 500, but the patient was developing symptoms of pancreatic asthma suggesting that the pancreas was being destroyed as far as the external secretion was concerned. When last observed 5 weeks after operation the blood sugar was still normal. The above response, i. e., failure of return of blood amylase to normal within several days, is so rare that the prognosis cannot be determined by past experiences. (Surg., Gynec. and Obst. 67: 31 (July) 1938.)

Pain which persists until shock supervenes is highly suggestive. While the pain is general in the upper abdomen, there is commonly a point of maximum tenderness about 5 cm. above the umbilicus. If the foramen of Winslow is open the irritating contents will spill into the general peritoneal cavity, otherwise this remains in the lesser omental sac.

Differential diagnosis may be very difficult and involve consideration of the corrosive poisons, coronary attacks, per-

The *treatment* is surgical, and operation should be done at the moment which seems best to the competent and experienced surgeon. Such a surgeon will allow no unnecessary loss of time in the fulminating case, will not hurry in the less acute case, and will not neglect suitable measures to combat shock, relieve emesis, and restore the acid-base balance.

The *surgical aims* are: (1) To complete the diagnosis by accurate visuali-

zation of the lesion, (2) to drain away any tryptic ferments by drainage of the lesser omental sac, (3) to decompress the pancreas by multiple nicking of the peritoneal covering of the gland, and (4) to decompress an obstructed pancreatic duct system by drainage of the biliary tract by the method that seems most appropriate to the patient's condition. The complications, which may be many and varied, must be treated as they arise.

Pancreatic Fistula

External fistula of the pancreas may be classified as either complete or incomplete. The former must be exceedingly rare, as the greater number of reports encountered in the literature deal with external fistula of the incomplete variety in which there is only a partial loss of pancreatic juice. Fistula of the pancreas arises in various ways:

- 1 Following a drainage operation on the pancreas for an acute inflammatory condition.

- 2 Rarely, as a result of a stab or gunshot wound of the abdomen.

- 3 From injury to the pancreas in operations on the kidneys, stomach and duodenum, biliary tract, spleen, retroperitoneal tumors, and adrenal glands.

- 4 After partial resection of the pancreas, or excision of an islet-cell tumor for the relief of hyperinsulinism.

- 5 Following operation for calculi of the pancreatic duct.

- 6 Most commonly, after an attempt to extirpate a cyst of the pancreas.

The recognition of uncomplicated pancreatic fistula is not difficult, it is established by means of examination of the fluid for its reaction and its enzyme content. Duodenal fistula may be differentiated by the additional presence of bile and by the erosion of the margins of the wound.

Treatment—The treatment of external pancreatic fistula is complicated first by the necessity of restoring pancreatic juice to the body in sufficient quantity and before serious physiological disturbances have taken place. Secondly, treatment is concerned with the attempts at closure of the fistulous tract. Conservative means should always be adopted in the beginning.

J. M. McCaughan and B. L. Sinner^{7,8} review the literature which deals with the various forms of medical treatment employed. They believe that if these measures fail after a reasonable trial period, radical treatment should then be considered. The operative procedure, the technic of which is described in a case report, consists essentially of *mobilization of the fistulous tract* and its *implantation* into the nearest portion of the upper gastrointestinal tract, preferably the stomach. The entrance of pancreatic juice into the stomach does not seem to have any deleterious effect on gastric digestion.

The authors report in detail a case of incomplete pancreatic fistula following a Billroth II gastrectomy for neoplasm of the stomach. Conservative treatment over a period of 8 or 9 months had failed to effect a closure of the fistula, or any significant diminution in the discharge from the fistula. They were able to inhibit or excite the flow with a number of drugs and food substances, but they question whether these effects could be maintained over long periods of time. High voltage roentgen therapy had proved unsuccessful in a previous case and so was not again attempted.

Operation consisted in the mobilization of the fibrous fistulous tract, including a cuff of skin about the external opening. The tract was inserted into the stomach through an opening in the anterior wall. The tract was not stitched

to the stomach wall, but was held in place, without tension, by the cuff of skin and the sutures closing the gastric opening, in addition to which omental tags were sutured over the site of implantation. The authors warn against angulations or constriction of the tract in order to prevent reduction and cyst formation. There was a postoperative leak of gastric and pancreatic juice for about 72 hours. This, however, cleared up completely, and the wound was entirely healed at the end of 4 weeks. The patient rapidly regained weight and strength.

Postoperative gastric analysis revealed the gastric contents to possess definite lipolytic activity. The degree of acidity, as compared with that before operation, was considerably lower. The authors believe this to be due to the fact that the principal acid-forming area of the stomach was unable to compensate in the usual manner. Blood diastase was normal.

Surgical Therapy of Hyperinsulinism

Hypoglycemia may be caused by disturbances of the physiology of the liver, the anterior lobe of the hypophysis, the adrenal cortex, the thyroid, the sympathetic nervous system, and the hypothalamus, and may also occur as a result of overactive islet tissue in the pancreas. The blood-sugar level is maintained as the result of an interplay of these same organs.

A. G. Whipple⁷⁹ shows that the characteristic syndrome of this condition consists of attacks of nervous or gastrointestinal disturbances coming on in the fasting state, associated with a hypoglycemia with readings below 50 mg. per cent, which is relieved immediately by the ingestion of glucose. Unless this triad is present, the patient should not be considered for operative therapy.

The nervous manifestations in these attacks may be grouped under 3 main heads: (1) Those related to disturbances of the sympathetic nervous system appearing as nausea, sweating, pallor, flushing, chilliness, and syncope; (2) those related to the central nervous system, manifested by restlessness, tonic or clonic muscle spasms, opisthotonos, and convulsions, and (3) those coming under the heading of psychic disturbances, such as apprehensiveness, confusion, disorientation, mania, unconsciousness, and coma.

In none of the proved islet tumor cases was the fasting blood sugar found to be above 60 mg. per cent.

The gross and microscopic picture of these tumors reveals (1) A diffuse hypertrophy or hyperplasia of the islet, (2) an adenoma of the islet tissue, and (3) carcinoma of the islet tissue. The most severe hypoglycemia was found in patients with carcinoma of the islet tissue. When more than 1 adenoma was found, a different arrangement could be seen in the 2 or more adenomas with varying amounts of degeneration.

There are many patients with mild hypoglycemia due to overactive islet tissue who respond to conservative therapy. The conservative measures may be divided into dietary and gland therapy. A diet which is low in carbohydrates and high in fat has been advised, as well as one which is high in protein.

Certain measures and technique for the surgery of islet tumors have been suggested; intravenous preoperative administration of 1000 cc. of 5 per cent *glucose in normal saline solution*, and *transfusion* if necessary, spinal anesthesia, but more often drop ether anesthesia; the curved transverse incision through both recti followed by the division of the gastrocolic omentum, which provides a free inspection of the entire pancreas. Islet tumors are most fre-

quently found in the tail or body of the pancreas, and if not easily found there the body should be mobilized and palpated; if they are not found in the tail or body of the pancreas, the duodenum should be mobilized and the head of the pancreas palpated. If 1 adenoma is found, careful search should be made for more; drainage is not necessary unless there is leakage of the pancreatic duct. If no tumor is found after a very complete exploration, the results in cases in which the body and tail have been resected are much better than those in cases in which a small portion of the tail has been removed. It is advisable to remove the spleen as well, in order to control hemorrhage. The bed of the pancreas should be drained after ligation of the pancreatic duct. The use of fine silk has been found satisfactory and will prevent the digestion of ligatures, which occurs when catgut is used in pancreatic tissue.

The finding and removal of all islet tumor tissue gives brilliant and lasting cures of the hypoglycemic state.

The author states that when an islet tumor was found and a partial pancreatectomy was done, poor results were obtained as a rule because of an overlooked adenoma or hyperplastic islet tissue.

There was a total of 56 cases in this series which were operated upon with disclosure of a tumor. There were 43 patients with islet-cell adenoma and 13 with islet-cell carcinoma. Of these, 5 died postoperatively and 5 died of other causes; 1 showed no improvement after 1 year and 4 gave insufficient data; 41 had relief of the hypoglycemia. Thirty-one patients had been followed for more than 1 year, and 7 were followed for a period of more than 5 years.

Of the patients in whom resection was performed and no tumor was found, 4 died postoperatively, 10 had complete

relief of symptoms, 4 showed improvement in their condition, 13 showed no improvement and 3 gave insufficient data. Eighteen additional cases of hypoglycemia with islet-cell tumor which came to autopsy are presented from the literature. Seven cases of hypoglycemia in which no tumor was found at autopsy are also presented. The author records the total number of operated cases in the literature, and reports the results obtained in these cases up to January, 1938.

Carcinoma of the Pancreas and Extrahepatic Bile Ducts

A group of 109 cases of carcinoma of the pancreas, and extrahepatic bile ducts, verified by operation or autopsy, has been reviewed by H. K. Ransom.⁸⁰ The disease occurred approximately twice as frequently in males as in females, and the average age of the patients was 56.9 years. Weight loss was the most common symptom; it was usually extreme, averaging 13.8 kg., and it occurred rapidly. Jaundice was the most common chief complaint and abdominal pain the most common initial symptom, the average duration of the symptoms was 5½ months; jaundice was the most common physical sign and was present in over three-fourths of the cases.

Courvosier's law was of relatively little value in making a correct diagnosis prior to operation, but it was of considerable value to the surgeon at the time of laparotomy, as it indicated the type of duct obstruction which was present. The operative findings proved the law to be accurate in over 80 per cent of the cases. Laboratory studies were of practically no value in diagnosis, while roentgenological studies were positive or suggestive in one-fourth of the cases. In the nonicteric patients the difficulties in diagnosis were greater than in the icteric group. In the former cases the condition

was most often confused with carcinoma of the stomach or colon. Evidence of antecedent infection of the biliary tract, as indicated by contraction of the gall bladder or thickening of its wall, was noted in approximately one-eighth of the operative cases, while calculi were present in the gall bladder in one-sixth.

Cholecystogastrostomy was regarded as the best palliative operation. The operative mortality for this procedure was 29.17 per cent. In 10 cases, according to the diagnoses made at the time of operation, the ratio of cases of carcinoma of the pancreas to that of the bile ducts was 2 to 1. Autopsy examination of these same cases proved that the ratio was 1 to 2. In 3 cases of carcinoma of the ampulla of Vater, transduodenal resection was performed, with 1 postoperative death and 2 recoveries. Hemorrhage was the most common cause of death following operation. The average duration of life following palliative biliary gastrointestinal anastomosis was 7.2 months in a group of 21 patients traced. Post-mortem examination showed the most common site of metastases to be the regional lymph nodes, while metastases to the liver and lungs occurred next in frequency. In the group of 30 cases examined post-mortem, there were 4 instances of multiple malignancy.

O. Rimpler¹ reports 3 cases in which carcinoma of the caudal portion of the pancreas was demonstrated either by necropsy or by biopsy. All the patients had hemorrhages into the gastrointestinal tract. There were hematemesis, melena and colics in the epigastric region. The author suggests 2 possible explanations for the gastrointestinal hemorrhages that accompany carcinoma of the caudal portion of the pancreas: (1) They may be due to diapedesis from congested, varicose veins of the mesen-

terium, stomach or duodenum. Necropsy in 2 of the cases revealed that the pressure of the primary tumor or of its metastases against the mesenteric root may readily cause such stasis and diapedesis. This mechanism is especially probable in late hemorrhages; that is, in those developing during the advanced stages of pancreatic carcinoma. (2) The hemorrhages into the intestine may be caused by intrapancreatic hemorrhage with discharge of the blood through the pancreatic duct. To be sure, in the 2 cases that came up for necropsy such hemorrhages could not be proved. The author suggests, however, that such hemorrhages should be looked for at necropsies. He emphasizes that in case of occult or manifest melena, particularly if it concurs with epigastric colics and if no source of hemorrhage can be found in the gastrointestinal tract (absence of enteritis and negative roentgenogram of the gastrointestinal tract), the possibility of a carcinoma of the caudal portion of the pancreas should be taken into consideration and an exploratory laparotomy should be made.

A case of carcinoma of the islands of Langerhans with hypoglycemia is reported by H. Joachim and M. M. Bano-witch.² Most of the numerous cases of spontaneous hypoglycemia due to pancreatic tumors reported in the past 10 years have been due to hyperfunctioning adenomas of the islands of Langerhans. Islet carcinoma as a cause of this syndrome has been relatively rare.

To the 7 cases previously reported the authors add another, which occurred in a woman 31 years of age. Vague symptoms had been present for 1 month, and recurrent convulsions and coma for 3 days. Laparotomy revealed a pea-sized indurated gland along the lesser curvature of the stomach, and in the terminal half of the pancreas a nodular mass about

the size of a tangerine, and several large glands. The spleen had to be removed to get at the mass in the pancreas. Only part of the tumor could be removed. Sections showed carcinoma of the pancreas with lymph-node metastases. Convulsions and coma occurred 4 days after operation and daily thereafter in spite of almost continuous glucose administration. The patient died 42 days after operation. The sella turcica was definitely small, but otherwise normal, roentgenologically. No autopsy was obtained and no attempt was made to demonstrate the presence of insulin in the tumor tissue.

STOMACH

Peptic Ulcer

A study of peptic ulcer based on necropsy records is given by S. A. Portis and R. H. Jaffe.⁸³ The topographical distribution of the ulcer found at autopsy is presented.

In a series of 9171 consecutive necropsies performed at Cook County Hospital from January 1, 1929, to December 31, 1936, there were 457 cases of all types of peptic lesions, or a total incidence of about 5 per cent.

The incidence of peptic ulcer in white people was found to be 5.23 per cent and in Negroes 3.5 per cent. The incidence of peptic ulcer is greater in the white male than in the white female, the difference according to sex is not as marked in Negroes.

There was definite evidence of activity of the peptic ulcers in 339 necropsies. In 118 cases peptic ulcer was the essential lesion, in 221 it was the incidental lesion. Therefore, the incidental lesion was almost twice as frequent.

When peptic ulcer was the essential lesion the duodenal ulcer predominated,

while when peptic ulcer was the incidental lesion the gastric ulcer predominated.

The peak for the incidence of peptic ulcer in the male is reached in the period from 51 to 60 years; the peak for the female is reached in the period from 31 to 40 years, while for the white female there is a second peak from 61 to 70 years.

Hemorrhage as a cause of death was observed in 0.43 per cent of all the necropsies and in 18.3 per cent in which peptic ulcer was seen as the essential lesion. Perforation was present in 20 per cent and stenosis in 7.5 per cent of all cases in which peptic ulcer was the essential lesion (120 cases). Therefore, more deaths were due to perforation than to hemorrhage in cases of peptic ulcer. Hemorrhage was observed most frequently in the stomach and perforation most frequently in the duodenum.

The peak of the incidence for peptic ulcer coincides with the age period accompanied by arteriosclerotic changes, when peptic ulcer is the incidental lesion it is most often associated with cardiovascular disease.

The predominance of scars and the examination of the tendency to acuteness and chronicity showed that gastric ulcer tends to be acute while duodenal ulcer tends to be chronic.

The following figures derived from private practice given by J. L. Kantor⁸⁴ show the incidence of ulcer as compared with other organic digestive diseases in 4000 patients: (1) gall-bladder disease, 307 cases (7.7 per cent); (2) duodenal ulcer, 296 cases (7.4 per cent); (3) gastric cancer, 85 cases (2.1 per cent); (4) colitis gravis, 59 cases (1.5 per cent); (5) gastric ulcer, 49 cases (1.2 per cent); (6) colonic cancer, 30 cases (0.7 per cent); (7) rectal cancer, 17 cases (0.4 per cent); (8) jejunal

ulcer, 9 cases (0.2 per cent). This may, therefore, be taken to represent the natural incidence of ulcer disease as seen in the living patient

Next is shown the incidence of the various types of ulcer, and how overwhelmingly frequent the duodenal lesion

Obviously, there is a discrepancy between the autopsy figures and those of the clinic. What is the reason for this discrepancy? Perhaps it is that the gastric lesion is not so vocal as the duodenal lesion. It is a matter of reasonably common knowledge that the symptoms of

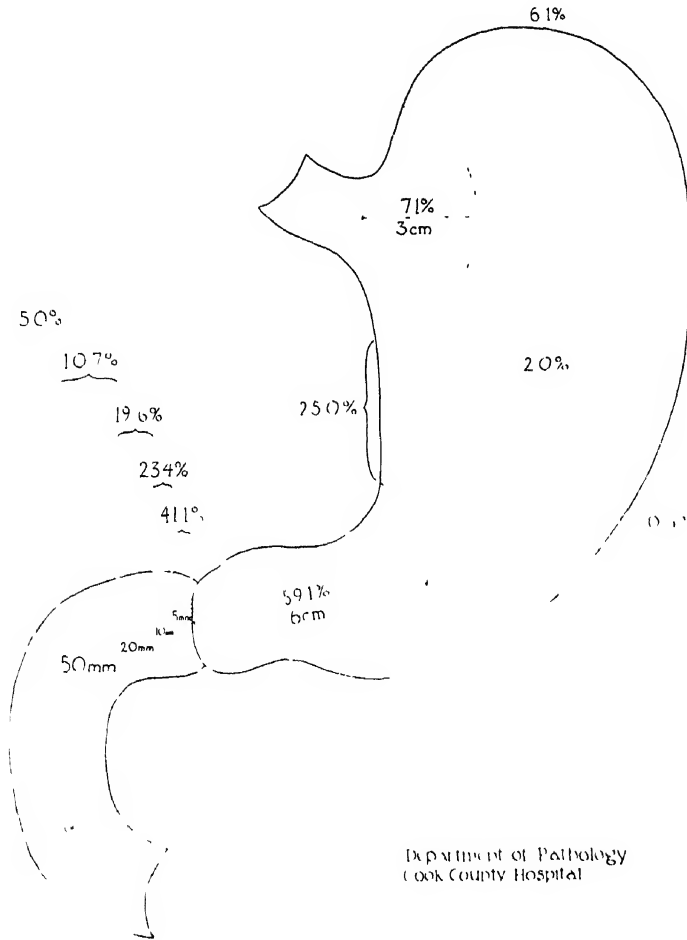


Fig. 61—Topographic distribution of 196 gastric and 158 duodenal ulcers
(J. A. M. A. 110: 6-13 (Jan. 1) 1938)

is compared with the other locations; esophagus, 1 case (0.2 per cent); stomach, 49 cases (13.8 per cent); duodenum, 296 cases (83.3 per cent); jejunum, 9 cases (2.5 per cent); Meckel's diverticulum, 1 case (0.2 per cent). The autopsies of Portis and Jaffe show that gastric ulcer actually occurs in about the same frequency as duodenal ulcer.

duodenal ulcer are more likely to be sharply defined than those of gastric ulcer. The pain is more regular and so are the relief factors. It has for some time been Kantor's impression that gastric ulcer is more frequently encountered as a surprise finding either at roentgen study, operation or post-mortem examination than is duodenal ulcer

Another possible reason for the difference is that an ulcer seldom kills a patient. Autopsy figures will therefore reveal all the patients who have had ulcer at any time in their lives, and hence the incidence, pathologically speaking, will be higher than it is clinically. Moreover, since some ulcers may heal without scars, the pathologic figures may even have to be increased to give the absolute incidence of ulcer disease. In order to show that ulcer seldom kills a patient, Kantor turns again to clinical experience. Known causes of death in 296 cases of duodenal ulcer were: Cardiovascular, 6, hemorrhage, 3, operation, 3; perforation, 2; carcinoma (gastric), 1; violence, 1. Known causes of death in 49 cases of gastric ulcer were: Operation, 4; carcinoma (in ulcer), 3, carcinoma (colon), 1; perforation, 1. In other words, only 16 of the 296 patients with duodenal ulcer were known to have died. Cardiovascular disease killed most of these and only 8 deaths could be attributed to the ulcer itself. Similarly, only 1 of the patients with gastric ulcer died of the ulcer proper.

Chronic Gastric Ulcer—The similarity of syndromes associated with benign gastric ulcer and benign duodenal ulcer has led to the thought that they are lesions of similar type. They differ, however, not only from the standpoint of the type of tissue in which the ulceration occurs, but also from that of the variable pathological nature of the lesions themselves, and from that of their response to both medical and surgical treatment.

W. Walters⁸⁵ states that of first importance, when a patient presents himself with a history suggesting benign ulceration of the stomach or duodenum, is that roentgenological examination be made by a competent roentgenologist to determine the exact situation of the le-

sion. If the lesion can be proved by roentgenological examination to be in the duodenum, and if a medical regimen is chosen for treatment, the possibility of the duodenal lesion's being or becoming malignant is practically nonexistent. In dealing with gastric ulcers at the Mayo Clinic, the author proceeds on the assumption that chronic ulcerating gastric lesions are malignant until they are proved to be benign.

Gastroscopy—The purpose of the article by R. Schindler and N. Giere⁸⁶ is to show the usefulness and value of gastroscopy to the surgeon. The following questions are discussed: Is a lesion of the stomach, which has been diagnosed by other methods, a benign ulcer or a carcinoma? Is cancer of the stomach operable? Of what value is gastroscopy in the early diagnosis of carcinoma, and may it improve the operative results? What are the reasons for the abdominal distress which so frequently follows operations for gastric lesions?

The article is based on the findings of 78 gastroscopic examinations carried out on 41 patients. Thirteen of the 41 patients underwent gastroscopy preceding operation, and 2 of the 13 patients again after operation. The remaining 28 patients were all examined postoperatively, 7 patients of this group again underwent operation after gastroscopy, and offered the opportunity for a biopsic control in 20 cases.

Although the gastroscopic diagnosis was confirmed in every one of the 20 cases in which a biopsic control was possible, it must nevertheless be admitted that negative findings in gastroscopy are not entirely conclusive.

The differential diagnosis between benign and malignant ulceration is not difficult after a gastroscopic examination by one trained in this field, even in the very early stage biopsy is not necessary.

EXPLANATION OF PLATE

A, gastroscopic picture of the penetrating benign ulcer of the lesser curvature of the stomach in case 4. The edge of the crater-like ulcer is sharp, and the cardiac part of its floor is brownish. Blood is shown oozing from the lowest part of the floor and accumulating in the dependent part (upward in the picture). The adjacent mucosa is excessively swollen and inflamed. Compare this illustration with figures 1, 2, 3 and 4.

B, gastroscopic picture of the infiltrating carcinoma with ulceration in the case in which operation was not performed. In the center of the picture there is a dark red ulceration. All the other parts of the stomach visualized with the gastroscope were stiff and infiltrated, and the surface was necrotic. The necrosis extended up to the cardia. Compare this illustration with figure 8. Gastroscopy proved immediately the inoperability of the tumor.

C, gastroscopic picture in case 7, showing ulcerative carcinoma. The ulcer is filled with brown clotted blood. The gray ridge discloses the malignant character of the ulcer.

D, gastroscopic picture, also from case 7, made 4 weeks after *C*. The ulcer as well as the niche (Fig. 5) were shallower, but at the pyloric side a nodular infiltration was seen. Compare this picture with figures 6 and 7.

E, gastroscopic picture in case 13, showing an ulcerated carcinoma around the pylorus with a sharply limited wall. The fold above the tumor is the "angulus." The whitish areas are remainders of food. Radical operation was possible. Compare this picture with figures 9 and 10.

F, gastroscopic picture in case 14, showing the patent gastro-enterostomy opening in the center. Intestinal juice flows into the stomach. At the side of the stoma there is a white ulcer larger than the stoma. A silk suture is seen coming out of the mucosa and hanging freely into the cavity of the stomach.

G, gastroscopic picture in case 21, showing the opening phase of the gastro-enterostomy stoma. The objective of the gastroscope is turned toward the anterior wall, the pylorus, which is well seen in figure 12, is not visible. The circular kerking folds of the jejunum are seen.

H, gastroscopic picture in case 26, showing a considerable portion of the jejunum in the right lower quadrant. About 2 cm. below the margin a crater-like deep ulcer is seen. The margin is partly covered with pus, and about it mucosal hemorrhages are seen.

(Arch. Surg. 35: 712-765, (Oct.) 1937.)

The differentiation between benign and malignant obstruction is more difficult but also possible. Gastroscopic diagnosis was proved to be correct in each of 7 cases. The gastroscopic picture is more characteristic than that of the gross specimen because of the presence of the circulating blood.

The operability of carcinoma was best determined by gastroscopy in 9 cases.

Special attention is called to the fact that operation for gastric carcinoma frequently results in a cure of long duration, particularly in cases in which the

diagnosis is made early. Early gastroscopy together with an early roentgenogram is capable of revealing operable carcinoma. Gastroscopy has proved to be superior to roentgen examination in certain cases, theoretically, roentgen examination should be superior in other cases. The 2 methods are not competitors; each supplements the other, and good co-operation between the gastroscopist and the roentgenologist is essential.

An unfavorable, diffusely infiltrating carcinoma of the body of the stomach



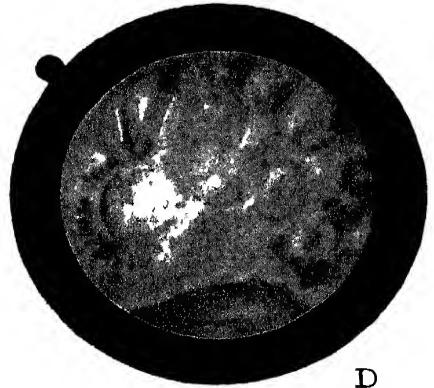
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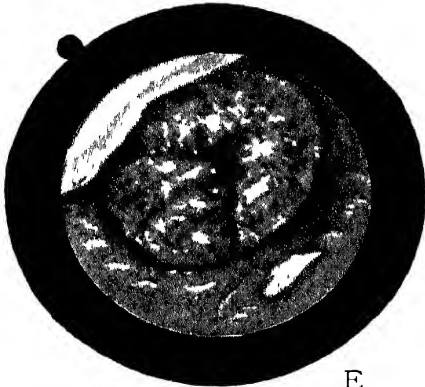
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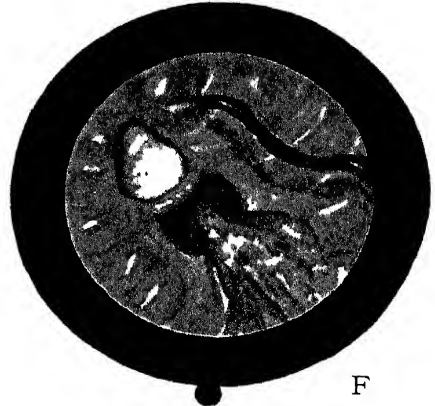
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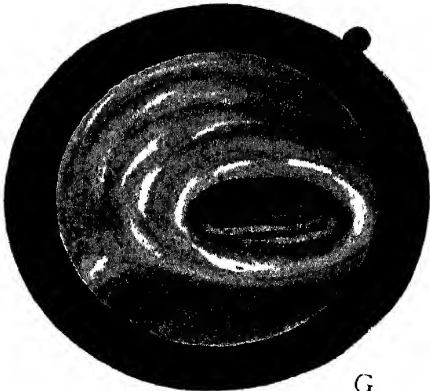
D



E



F



G



H

PLATE

should be recognized by gastroscopy and excluded from operation. Exploratory laparotomy should be done only in those relatively few cases in which the operability of the lesion is not definitely determined by gastroscopic examination. This will result in a greatly lowered surgical mortality and will help to dispel the prejudice which so many hold in respect to the surgical treatment of carcinoma.

The artificial stoma was seen with the flexible gastroscope in 12 cases after resection and in 15 cases after gastroenterostomy; it was not revealed in only 3 cases in which gastroenterostomy had been done, or 10 per cent of all the cases seen after operation. The finding of the stoma, however, is not easy, the correct instrument must be chosen in respect to the peculiarities of the individual case. A relatively normal stomach was seen in only 3 instances (10 per cent). Recurrent ulcer was found in 1 case and a jejunal ulcer in 2 cases, the ulcer was probably missed in 1 case. Simple hemorrhagic erosions were observed twice. Silk sutures which had cut through the mucous membrane and were hanging free into the gastric cavity were observed in 3 cases. The most frequent disease of the stomach after operation was chronic gastritis, it was observed in 15 cases. Gastroscopic examination was unsatisfactory in 4 cases. An artificial stoma after resection or gastroenterostomy may remain patent or may acquire pylorus-like rhythmic activity. Four stomas of the latter type were seen, 2 after resection and 2 after gastroenterostomy. It seems quite certain that this pylorus-like adaptation protects the stomach against the development of post-operative gastritis. Although it is not known what conditions favor this development after resection, it does seem that gastroenterostomies which are carried

out in the posterior wall near the pylorus and close to the greater curvature have a greater tendency to bring about this adaptation. Silk sutures which have not been expelled into the cavity of the stomach several months after operation should be surgically removed since they irritate the mucous membrane and cause chronic gastritis with painful erosions, and may even play a part in the development of jejunal ulcers. High voltage roentgen therapy by the Coutard method causes severe gastritis in the stomach after operation just as it does in other mucous membranes.

Complications of Peptic Ulcer—

Perforation—The experience of G. Boneo and E. A. Ramirez⁸⁷ is given in 85 cases of gastric duodenal perforation. All patients but 1 were men. The authors conclude that perforation of gastroduodenal ulcers takes place almost exclusively in men ranging in age from 30 to 40 years, after which it is rare. Perforation occurs more frequently in gastric than in duodenal ulcers and is most frequent in autumn and winter. In the group of patients seen by the authors, perforation took place within the third and sixth hours after ingestion of food or fluids. There was a history of gastric or duodenal disturbances in 94 per cent of the cases. The treatment is surgical and urgent. It consists in simple suture of the perforation, with omentoplasty and without drainage, in patients in good general condition, with short hours of evolution of perforation and who do not show symptoms of peritoneal contamination. Otherwise a local or suprapubic drainage is left. Mortality increases in relation to the age of the patient and to the hours elapsed between the time of the perforation and the surgical intervention.

A series of 170 acute, perforated ulcers treated on the First Surgical Division

of Bellevue Hospital, between 1920 and 1936, is presented by J. A. McCreery⁸⁸ The predominance of perforations on the anterior surface of the stomach and duodenum is emphasized, as is the relative infrequency of this condition in the female. The importance of early diag-

gave better results, it is the author's belief that closure alone is the more satisfactory procedure; the alternative in occasional cases with extensive induration making closure difficult—when the patient's condition justified it—being a partial gastrectomy.

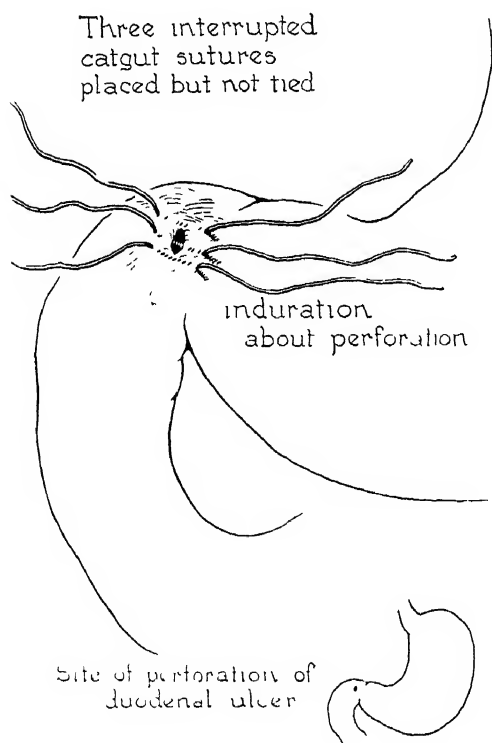


Fig 62

Fig 62—The placing of sutures in relation to perforation (Graham Surg Gynec and Obst 64 235-238, 1937)



Fig 63

Fig 63—Sutures tied over free omental graft. No attempt is made to close the perforation by the suture. They are tied only sufficiently tight to hold the graft *in situ* (Graham Surg, Gynec and Obst 64 235-238, 1937)

nosis and operation is again stressed by the mortality percentages. An analysis of 35 patients that died in the series is shown in Table IV.

The difficulty in determining the final results is shown by the cases returning in 10 or more years after perforation with recurrence of symptoms.

While the percentage results in the follow-up of a few cases would tend to show that closure plus gastroenterostomy

Closure alone may necessitate more secondary operation, but will lessen the number of serious secondary procedures such as secondary gastrectomies for marginal ulcer, a procedure which taxes the skill of the most experienced surgeon as well as the resistance of the best prepared patient

L. S. Fallis⁸⁹ reports a mortality rate of 20 per cent in his series of 100 cases of perforative peptic ulcer, but in the

TABLE IV
ANALYSIS OF THE 35 PATIENTS THAT DIED

Time Between Perforation and Operation	Recoveries	Deaths	Mortality Percentage
1 to 6 Hours	87	4	4.3
6 to 12 Hours	32	8	20
12 to 24 Hours	9	5	35.7
24 to 48 Hours	3	12	80
48 Hours and Later	2	3	60
No Operations	5	3	37.5

last 10 years has been only 11.9 per cent. He attributes the improved results to better postoperative treatment, including the routine use of blood transfusions and gastric suction. Gastroenterostomy and other gastric operations were performed on 14 per cent of the patients, with a mortality rate of 14.3 per cent, while the mortality rate for simple closure was 18.1 per cent. In spite of these figures simple closure is recommended.

Hemorrhage—In an attempt to obtain a clearer conception of the indications for the surgical treatment of bleeding peptic ulcers, L. Goldman⁹⁰ analyzed the 1025 entries to the San Francisco Hospital of 890 patients with peptic ulcer. Of 349 patients who entered the hospital because of gross hemorrhage from peptic ulcer or in whom this complication developed during their period of hospitalization, 39 died of exsanguination, while an additional 13 died of conditions associated with the bleeding. The study suggested that the occurrence of hemorrhage, similar to that of perforation, is rare in patients following prescribed or proper diet-alkali therapy. In the majority of cases, dietary or alcoholic indiscretion precedes the onset of these complications. In the few patients who are following adequate treatment at the time of the onset of the hemorrhage, surgical treatment should be considered during the quiescent stage. If surgery

is performed for the bleeding type of ulcer, direct attack on the ulcer with its removal, in addition to subtotal gastrectomy, is the procedure of choice and is more likely to reduce the incidence of hemorrhage after surgery. Gastrojejunostomy may not protect against the recurrence of or subsequent hemorrhage from a duodenal ulcer. Thirty patients of the series had gross hemorrhage from ulcer after gastroenterostomy. Patients with no or a short history of peptic ulcer in whom hemorrhage develops suddenly have the poorest prognosis for life in the entire series. Transfusions are important in the treatment of this particular group. Surgery is not feasible in the acute stage because of the patient's poor general condition. After the hemorrhage has ceased, these patients usually do well on medical treatment. About 62 per cent of the patients with hemorrhage have had symptoms of ulcer for many years and represent an uncooperative group of patients. If, during the acute bleeding phase, hemorrhage keeps recurring while the patient is under medical treatment, with transfusions, immediate surgery should be considered. Conservative treatment is indicated in patients less than 40 years of age without arteriosclerosis.

Indications for Surgical Treatment of Gastric Hemorrhage—H. Finsterer⁹¹ summarizes his point of view on the treatment of gastric hemorrhages as follows:

1. In acute hemorrhage from a definitely demonstrated ulcer, he advises immediate operation because that is the most reliable method for the arrest of the hemorrhage. It prevents fatalities resulting from later erosion hemorrhages due to a burrowing ulcer and it also prevents perforation into the free abdominal cavity. A preoperative or postoperative blood transfusion is necessary only in

severe hemorrhages resulting from erosion of a large artery

2. If after failure of internal treatment an ulcer persists in bleeding, the author recommends late operation. In cases in which it is doubtful whether the hemorrhage persists, he recommends an expectant attitude, because the prolonged anemia has so impaired the internal organs that even after blood transfusion the operation may be a failure.

3. In case of acute hemorrhage from a probable ulcer he recommends an exploratory laparotomy under local anesthesia, so as to exclude a penetrating ulcer. If an ulcer is detected, the resection should be done in the typical manner. In case of a hemorrhage that is the result of an erosive gastritis, the resection is advisable if the disorder has existed for many years and relapses constantly; otherwise the abdomen is closed and the internal treatment is continued.

4. If the hemorrhage appears suddenly, without the slightest previous disturbances, an acute, flat ulcer is probably the cause. In this case internal treatment is advisable. If the loss of blood is considerable or the hemorrhage recurs, the internal treatment should be supported by a blood transfusion.

5. If the existence of a hepatic cirrhosis is certain, exploratory laparotomy seems advisable, if only the slightest gastric disturbances (*e g*, heartburn) have preceded, because, on account of the stasis, the patient may bleed to death even from an eroded vein of a flat ulcer.

6. When hemorrhage occurs in elderly patients (beyond the age of 60 years) or in an existing arteriosclerosis, the author considers surgical treatment even more urgent than in young persons.

According to R. R. Graham,⁹² it seems trite to state that not all hematemesis is the result of an ulcer in the stomach or duodenum. The clinician's primary

responsibility to a patient suffering from hematemesis is to exclude lesions other than ulcer which might be the cause.

Granted that the diagnosis of a *duodenal ulcer* accompanied by massive hemorrhage has been substantiated, what is our responsibility? Graham does not believe that in the young patient a single massive hematemesis is sufficient justification for operation. The recent survey of Dr. Allen of the Massachusetts General Hospital in Boston, together with the experience of Mr. Gordon Taylor of the Middlesex Hospital, has impressed upon all who are interested in this problem that there is a very definite difference in the seriousness of massive hematemesis in patients under, as opposed to those over, 50 years of age.

Graham does not feel that he has had sufficiently extensive experience to make any statement in regard to the wisdom of immediate operation for hematemesis upon patients who are candidates for such therapy. A recent experience, however, has confirmed the statement which Mr. Gordon Taylor has emphasized on more than one occasion, namely: "If one is going to carry out an emergency surgical procedure for massive hematemesis, it had better be done within the first 48 hours, or a fatality will result, even though by means of the continuous transfusion, as advised by Marriott, the hemoglobin has been brought up to 80 per cent."

In Graham's recent experience, he had a patient admitted 1 week after a massive hemorrhage from a duodenal ulcer, in which the hemoglobin was down to 30 per cent. By means of continuous transfusion, his hemoglobin was restored to 60 per cent, at the end of which time he had a further massive hemorrhage, and the hemoglobin fell again to 45 per cent. Further transfusion and operation were followed by a fatality. This is a typical

sequence of events, which Gordon-Taylor has warned us against, and Graham's only justification for considering operation on such a patient was his firm conviction that he had no choice but to lose the patient without an effort, or to run the remote chance that such a procedure might save his life.

Graham counsels, however, that in the young individual, a single massive hemorrhage is not sufficient indication to warrant either an immediate or a subsequent operation, but in the older individual (over 50) where there has been a hemorrhage of sufficient volume to lower the hemoglobin below 50 per cent, operation should be seriously debated before dismissing this patient to a purely dietetic regimen. Graham believes that the source of such massive duodenal hemorrhage is from a duodenal ulcer situated on the posterior wall and communicating with the pancreaticoduodenal artery or one of its branches. As a result of this belief, Graham states that he must question the wisdom of any surgical procedure which is not accompanied by ligation of this blood supply. As a corollary, such a procedure must be accompanied by a resection of the pyloric end of the stomach. While Graham has carried out indirect types of operative procedures on a small group of patients and the patients have recovered, this has been done only because he was fearful of a more formidable procedure, and it is in this decision that the judgment and experience of the surgeon account for so much. As a fundamental principle, Graham feels that whenever operation is indicated, if it is deemed wise and possible, the radical and direct attack upon the source of the bleeding should be carried out.

Prior to 1931, all patients who were being prepared for operation following a massive hemorrhage were fed very

cautiously and in small amounts a bland diet of milk and foods made from milk. In September, 1931, a patient was admitted after a massive hemorrhage, but the usual dietetic control was accompanied by further hemorrhage. Transfusions were used, in volume from 250 cc. to 1000 cc. at intervals of a week to every other day. After 2 months Lewis suggested that the patient could be made no worse and at least his hunger could be assuaged by a more liberal diet, and if there were in addition an abundance of animal protein, the resulting stimulus to hemoglobin formation might be beneficial. This was carried out, and the spectacular rise in the hemoglobin and the improvement in the patient's condition were delightful.

Since this experience Graham and his associates have rapidly increased the diet of patients recovering from massive hemorrhage from duodenal ulcers. Now by the fifth to the sixth day after the violent bleeding has ceased, these patients are on a generous and varied diet containing an abundance of meat, eggs, fish and fowl, the only safeguard being that the vegetables are puréed and the meats are minced. In addition the administration of reduced iron is believed to be very beneficial.

Treatment—The treatment of gastric ulcer is dependent on several factors, among which are (1) The duration and type of symptoms, (2) the healing of the lesion, or its failure to heal under a medical regimen carried out in a scientific fashion; (3) the presence or absence of a crater, especially with respect to bleeding, and (4) the presence or absence of pyloric obstruction.

When the symptoms have been of short duration and the ulcer is small, every attempt should be made to induce healing of the lesion by nonsurgical means. When roentgenological examina-

tion discloses that the ulcer has a demonstrable crater, especially when episodes of bleeding have occurred, when the lesion is producing pyloric obstruction, or when it is prepyloric in situation or is on the greater curvature, generally speaking, **surgical removal** of the lesion should be undertaken without delay. The fact that an ulcer of the stomach is reported by the roentgenologist to be probably benign, does not exclude the possibility that the lesion is carcinomatous. The roentgenologist wishes such an opinion of his to be considered only as a contribution to the final diagnosis.

In experience at the clinic, each year a considerable percentage of patients operated on for carcinoma of the stomach have related, in their early histories, symptoms indistinguishable from those of benign ulceration.

C. W. Cutler, Jr.,⁹³ points out that it is of interest to observe that year by year the number of operations performed for chronic ulcers of the stomach and duodenum has gradually diminished, and this is without a significant diminution of the number of cases admitted. In 1926 there were 46 such operations, in 1936 but 12. This change has been due primarily to the increasing recognition of the fact that careful medical management is capable of relieving or controlling a considerable number of these cases. Surgery is indicated only in cases in which the medical regimen has failed or in which complications have resulted. All cases of chronic peptic ulcer are now considered as medical problems primarily and the patients are admitted directly to the medical wards. Not only is no patient now operated on at the Roosevelt Hospital for chronic peptic ulcer without having had a thorough, controlled and efficient course of medical management, but each patient for whom operation is proposed must be passed on

by a "court" consisting of physician, surgeon, gastroenterologist and roentgenologist. The type of operation to be employed in each case is determined by certain guiding principles: (1) The operation must be of such a nature that the particular patient can tolerate and survive it. (2) Not only should it aim at alleviation of symptoms, but it should give freedom from likelihood of recurrence or of complications, both early and late. (3) The ideal procedure having been determined, it should be abandoned or modified if the condition found at operation warrants. The pursuit of the foregoing policies and practices is encouraged by the early results in the present group of cases. The 14-year period covered by the report shows a mortality in Polya and Billroth II resections, for all types of primary peptic ulcer, of 9.3 per cent. This compares favorably with the 8.5 per cent mortality of gastroenterostomies during the same period, when one considers the 16 per cent of recorded late poor results with gastroenterostomy, as against the 3 per cent of poor results with resection. These figures do not take into account the cases of secondary complications.

Indications for Operation in Cases of Gastric Disease The common indications for operations in chronic duodenal ulcer, aside from those complications which may of themselves clearly call for operation, are chronicity and sufficient severity of symptoms which cannot be controlled by adequate medical treatment. In addition, the age, sex, occupation, and disposition of the patient must be taken into consideration, because all these factors influence the result of any form of treatment.

According to D. C. Balfour,⁹⁴ there are certain general principles in the management of duodenal ulcer which have become well established. Since it is not

a malignant disease, and since the serious complications are relatively rare, emergency measures are required only in the event of acute perforation. In a large percentage of cases of duodenal ulcer, the disease may be controlled by adequate medical management.

The fundamentals of treatment have not materially changed. *Frequent feedings* of an adequate amount of food have been shown to be very important, and Mann has demonstrated, in dogs, that feeding at frequent intervals is a major factor in controlling gastric acidity. More recent developments in medical management have been the use of such buffer agents as mucin and the use of extracts of duodenal mucosa; the latter has been shown experimentally to have an inhibitory action on gastric secretion. The early reports of the results of any treatment of duodenal ulcer must take into consideration the prompt relief of symptoms, which usually comes only from rest.

Surgical treatment of duodenal ulcer in its early stages may be indicated in those cases in which symptoms are severe and do not respond to treatment, or the patient is unwilling or unable to persist in a satisfactory regimen. In such cases (because the patient is young, there is usually no motor impairment and gastric secretion is hyperactive) gastroenterostomy should be avoided, for the incidence of jejunal ulceration is high in such circumstances.

The results of the surgical management of duodenal ulcer will depend to a large extent on the skill with which cases are selected for operation.

The general principles of management are secondary in importance to the selection of patients for operation for duodenal ulcer. All surgical procedures have a common purpose, that is, to modify gastric function, and apparently the

results of operation are in direct ratio to the degree that gastric function is modified, particularly in its secretory mechanism. At the same time, the ideal to be sought for would appear to be to modify gastric function only sufficiently to cure the ulcer and to prevent the recurrence of the disease.

Partial gastrectomy and *posterior gastroenterostomy* are the most effective procedures in the treatment of duodenal ulcer.

The second general principle of surgical management for duodenal ulcer involves operations on the outlet of the stomach in an endeavor to modify gastric function by permanent ablation of the pylorus.

The first indication for operation in *gastric ulcer* is that, regardless of the history which the patient may present, if the lesion which is demonstrated roentgenologically does not heal satisfactorily in a reasonable length of time by medical treatment, the surgeon is not fulfilling his responsibility unless he advises the patient to have the lesion removed. The chief advantage is that the small gastric ulcer can be removed satisfactorily by either knife or cautery, the defect closed, and gastroenterostomy performed with every assurance of an excellent and permanent result. This type of operation, namely, excision and gastroenterostomy, is an ideal procedure for the small gastric ulcer.

When ulcers are situated in the upper segment of the stomach, operation perhaps should not be advised so readily, and more intensive and prolonged medical treatment may be justified. The lesions in the upper part of the lesser curvature, however, usually can be dealt with directly by local excision after the lesser curvature has been mobilized by the division of inflammatory adhesions which are routinely found in such cases.

When partial gastrectomy can be done with little more risk than excision and gastroenterostomy, it can never be condemned for gastric ulcer. It is important to remember that gastroenterostomy alone for gastric ulcer has proved in many cases to enhance the capacity of healing the lesion, provided of course it is not malignant.

The indications for operation in cases of *benign tumor* are clear when they have been demonstrated roentgenologically. When a tumor which has been responsible for bleeding is visualized roentgenologically, the indication for removal is clear since the operation can usually be done satisfactorily without more than incidental risk. The chief indication at operation in such cases is to be aware of the fact that these tumors may be multiple even though only a single lesion has been demonstrated by the roentgen rays.

Diverticulum of the duodenum is not of great surgical importance because of the rarity with which operation is indicated in such cases. It is only when such diverticula are of great size, or in very rare instances in which complications have occurred, that any surgical procedure should be seriously considered.

In this country very little interest has been shown in the proposal of gastric resection for *gastritis*. From a surgical standpoint, gastritis is more a problem of academic interest, that is, the relation of gastritis to ulcer and gastric cancer, and its place as a factor in disappointing results after operation. The general impression among clinicians at the moment is that the condition is one which usually can be remedied easily by suitable medical management, and there is an increasing possibility of diagnosing the condition both by its clinical manifestations and by means of the gastroscope and fluoroscope.

Indications for operation in cases of *cancer of the stomach* depend on many factors, and, first, on whether or not a positive diagnosis can be made. The profession is well aware of the danger of dealing with a small cancer of the stomach on the assumption that it is a gastric ulcer, but the very fact that this is now well known has greatly decreased the number of such cases.

The frequency with which cancer, as we see it, develops in gastric ulcer must be comparatively small because of the high incidence of cancer of the stomach and the relative rarity of gastric ulcer. The question of advising operation for a small gastric lesion which has all the appearance of being an ulcer on the score that it may be malignant will have to be determined chiefly by the degree of distress that the patient is having from the ulcer, the amount and kind of treatment he has had for it, whether or not by roentgen examination there are signs of healing, and the risk of a surgical procedure. Unless symptoms are quite uncontrollable by medical treatment, and unless unquestionably adequate treatment has been applied, these small gastric lesions should be under the observation of a physician who can and will institute intensive medical management, who will be conscious of the possibility of the lesion actually being malignant, and who will, therefore, keep the patient under close observation from a clinical and roentgenological standpoint.

Another group of cases in which there is some uncertainty on the score of diagnosis is that in which symptoms may arouse suspicion that malignant disease is present, but in which the latter fact cannot be confirmed roentgenologically. In the records of the clinic from 1906 to 1931 only 25 patients were sent to the hospital for operation because of a clinical diagnosis of cancer of the stom-

ach when the roentgenologist reported a negative stomach. No better evidence of how the expert roentgenologist can convince the surgeon of the accuracy of his method can be found than this.

In addition to this group are cases in which patients were operated on for other abdominal conditions, and in which cancer of the stomach was encountered although the roentgenologist's study of the stomach had been negative. A further debatable group, insofar as uncertainty of diagnosis is concerned, consists of those cases in which spasm either of the antrum or pylorus appeared to represent an organic lesion and in which a diagnosis of cancer of the stomach was made but could not be confirmed by the consulting roentgenologist. Finally, there is the group of cases in which the expert roentgenologist finds sufficient rigidity of the musculature of the stomach, along with superficial ulceration, to justify the statement that malignancy cannot be ruled out. Such patients should be kept under the closest observation and be repeatedly examined roentgenologically, and if the deformity persists exploration should be advised. In the much larger group the diagnosis of cancer is all too clear, and the question to be decided is whether or not exploration is justifiable.

Among contraindicating factors is a diagnosis by the roentgenologist of a frankly *inoperable* cancer. The surgeon will have in mind the fact, however, that the nature of the cancer, even though it seemed to the roentgenologist to involve too great an area of the stomach, may make possible an extensive resection with some possibility for cure, or a great probability of real palliation. The investigation for evidence of *metastasis* should be most thorough, as the end results of operation for cancer of the stomach depend to a considerable extent on whether

or not metastasis has been meticulously searched for prior to operation. The rectal shelf, the supraclavicular notch, and the occasional thoracic metastatic lesion may easily be overlooked in an incomplete examination.

Having eliminated the possibility of distant metastasis, examination of the tumor, when it is palpable, will disclose findings of importance. Its size is of importance since the significance of a large mass may be much exaggerated; some of the most favorable cases for cure are those of large colloid and well demarcated tumors. A much more important sign than size is the mobility of a tumor, particularly its lateral mobility. Severe pain is of serious import since it usually denotes involvement of the peritoneum. Rapid loss of weight in the absence of obstruction of either cardia or pylorus and any suggestion of icteric sclerae are not encouraging features. Marked secondary anemia in the absence of gross hemorrhage is also an unfavorable sign. The factor of age is important since in the more advanced years there should be less inclination to resect the stomach in those cases in which the lesion is very extensive.

For those lesions which are known to be extensive, and when there is involvement of the stomach, a *left rectus incision* has very definite advantages, while in other cases a midline incision is usually as satisfactory as any. If there are no evidences of peritoneal implants, the *incision* should be of sufficient size to admit the hand, enable thorough exploration to be made, and make possible satisfactory mobilization of the stomach.

In respect to the lymph node, unless it can be proved that enlarged lymph nodes outside the range of removal are malignant and that there is other evidence of distant metastasis, it may be

assumed that it is possible that these lymph nodes are only inflammatory, and resection can be carried out

In the largest group of cases of cancer of the stomach, a decision can probably be made in respect to confirming the diagnosis and determining the best method of management. In the case of larger tumors it may first appear that removal is not feasible. As a matter of fact, the survival rates among patients with large lesions as contrasted with those with small lesions showed at the end of 7 years that 33 per cent of the former were alive whereas only 24 per cent of the latter were alive.

If exploration discloses a small nodule in the liver or an implant on the rectal half, experience has shown that it is frequently to the advantage of the patient to perform palliative gastrectomy. When there is any indication of diffuse abdominal metastasis and when free fluid is present, any type of palliative operation is of questionable value except, possibly, when a high degree of pyloric obstruction is present, but even then gastroenterostomy is likely to prove disappointing in its effect in relieving the obstruction. Lesions that are more or less confined to the antrum are usually resectable unless extragastric involvement precludes removal of all malignant tissue. Extension up along the lesser curvature, particularly in the scirrhus type of cancer, is all too frequently the reason for inoperability.

A very important group of cases is that with circumscribed growths high in the fundus which are chiefly on the posterior wall and greater curvature, for in these cases local excision can frequently be done with as good prospects of cure as with extensive gastrectomy. When small lesions are readily accessible, they should be removed either by local excision and gastroenterostomy,

or by gastric resection, but when they are so located that their removal would entail a great risk, it is often better to assume that they are benign and perform only gastroenterostomy.

When gastric resection is advisable, the methods by which it is carried out will vary with the preference of the surgeon, the location and extent of the growth, and the technical difficulties encountered. When recurrence takes place after the Billroth II procedure or any of its modifications, mechanical difficulties are not frequent, and for this reason the Billroth II procedure is preferable for cancer.

When any technical difficulties are encountered in the Billroth II operation because of obesity or a short mesocolon, an anastomosis in front of the colon has very definite advantages. Of the palliative procedures, by far the most important is that by which the growth is completely excluded. This can be accomplished by employing the exclusion operation recommended by Deyme for duodenal ulcer which, in suitable cases, is an extremely valuable palliative measure in cancer. It affords complete relief from the actual or impending obstruction and results in very definite prolongation of life in comfort. Palliative gastroenterostomy is now generally recognized as too frequently being disappointing and is indicated but rarely.

With modern diagnostic methods, as a result of which cancers are seen in their earlier stages, the operability rate is about 43.5 per cent for those cases in which exploration is carried out, and the mortality in those cases in which resection is carried out is between 10 and 13.9 per cent. The chief cause of death remains rather consistently peritonitis or pneumonia, or both, since either one or both of these conditions

are present in 70 per cent of the cases in which death occurs.

When partial gastrectomy is possible, regardless of the degree of involvement of lymph nodes, the extent of resection, or whether the procedure is done as a palliative measure, approximately 32 per cent of the patients are alive and well 5 years after operation.

Subtotal Gastric Resection for Peptic Ulcer—While an increasing number of surgeons are advocating subtotal gastric resection as a routine procedure for cases of peptic ulcer, G Miller⁹⁵ points out that many are still satisfied with the results of the palliative operations such as gastroenterostomy, especially for duodenal ulcer. Nevertheless all gastric surgeons use resection for certain types of ulcer such as pyloric ulcer with a suggestion of cancerous change, and for marginal ulcer. When any such technically difficult surgical procedure becomes more widely used, the average results become less satisfactory. This is natural as more surgeons attempt a procedure with every detail of which they are not familiar, and may even not have grasped the fundamental principles on which the operation was designed. There are 2 very important factors in gastric surgery, first, the ability to relieve the patient of all symptoms permanently, second, the mortality following such operations.

The purpose of this article is not so much to add to the controversy regarding the choice of operation, but rather to discuss resection from the point of view of mortality. Advocates of resection believe that the chronicity of ulcer is due to the corroding action of the acid chyme and that the way to cure the ulcer permanently is to remove as much as possible of the acid-secreting portion of the stomach so that achlorhydria or hypoacidity remains. This means a sub-

total resection with the removal of two-thirds to three-quarters of the stomach. Surgeons who remove little more than the pyloric antrum (the alkaline-secreting part of the stomach) and expect a high percentage of 5-year cures, will be woefully disappointed, and the figures will be used by others to discredit the procedure. In every large general hospital where many surgeons are operating, the difference in technic between the various surgeons is quite striking, and these differences must be reflected to some degree in the mortality and the end results.

It may be stated that if surgery is going to cure ulcer it must be adequate surgery. The surest way to keep down acid (the agreed cause of chronicity) is to remove as much as possible of the acid-secreting portion of the stomach. Do a gastroenterostomy and a certain percentage of marginal ulcers occurs. Add an enteroenterostomy (leading the alkaline neutralizing fluids of the duodenum away from the stoma) and you more than double the incidence of marginal ulcer. The jejunal mucosa can no longer resist the corroding effect of the acid chyme. Given a patient with hyperacidity over 100, cure is impossible until achlorhydria or at least a low acid is obtained.

Gastrojejunostomy—An essay by P. E. Truesdale⁹⁶ includes his experience in the surgical treatment of ulcer with not only gastrojejunostomy, but also the other types of surgical intervention. Postoperative results have demonstrated to Truesdale that "the gastrointestinal tract is a one-way canal. Gastroenterostomy is a rational operation when the pylorus is stenosed by the cicatrix of an old ulcer. This operation is illogical when it leaves 2 openings, both of which continue to function."

Lahey's discussion of this paper is of great interest in that he believed that gastroenterostomy as a routine procedure for duodenal ulcer is today unjustified. There are too many gastrojejunal ulcers. While one cannot definitely state what the accurate percentage is, it is too high to justify the method as a routine operative measure with which to treat surgical peptic ulcer. Despite this criticism, however, there are cases in which gastroenterostomy must be employed. It may be used in the "bad risk" patient who cannot tolerate the ideal procedure of subtotal gastrectomy. There are, in addition, certain individuals, notably people past middle life with cicatrizing chronic ulcers at the pylorus producing obstruction and with relatively low acid content, who respond very well to gastroenterostomy. However, in the young individual who has a high acid content and prospect of a long life and does not have pyloric obstruction, gastroenterostomy frequently only adds to the ultimate seriousness of the ulcer situation. It is in these cases that subtotal gastrectomy is strongly advocated.

Moreover in 17 cases in which resection for exclusion was performed, in which the duodenum and the ulcer were undisturbed, and in which a high resection had been done, the "follow-up" showed end results quite as satisfactory as in those cases in which the duodenum was removed.

It is of interest to note that B. Newburger,⁹⁷ in an analysis of 137 cases of benign and malignant conditions of the stomach and duodenum, reports 31 gastroenterostomies performed for benign lesions, 48.3 per cent of which were followed by jejunal ulcers, and the author concludes, "because of the extreme frequency of jejunal ulcer, gastroenterostomy should be discarded as a method of treatment for gastroduodenal

ulcer except for a small strictly selected group. Resection and resection for exclusion should be the methods of choice."

Gastrojejunal Ulcer

The results obtained in 208 surgical interventions done by H. Finsterer⁹⁸ on patients with gastrojejunal ulcer are reported. There were 203 radical operations. The surgery done previously, or at the first operation, was posterior gastroenterostomy in 126 cases, anterior gastroenterostomy with enteroanastomosis in 19, pyloric exclusion in 12, resection for exclusion in 8, pyloric gastric resection in 29, and a radical operation for gastrojejunal ulcer in 14 cases. Four of the resections for exclusion and 4 of the pyloric resections had been done by the author.

Most of the patients, 74.5 per cent, were under 50 years of age, and after the sixtieth year only the most urgent indications, such as hemorrhage, perforation, or colon fistula were considered surgical indications. There were 14 patients over 60 years of age who were operated upon with 4 deaths.

Following gastroenterostomy the patients were operated upon as soon as possible after the marginal ulcer appeared. Medical management was tried first in those cases which occurred after resection, because in this type of patient healing may follow. In the radical operation at least two-thirds of the stomach, the old duodenal ulcer, the pylorus, and the loop of bowel used for the original anastomosis were resected, then the jejunal loops were anastomosed end-to-end and the stomach anastomosed to the jejunum end-to-side by a modified Hofmeister-Finsterer procedure.

However, the Billroth I anastomosis, or the Haberer modification, (terminolateral gastroduodenostomy) between the duodenum and the stump of the stomach

was used only in the nonpenetrating type of ulcers, in cases with a wide duodenum and a ptotic stomach. Despite these precautions this procedure had a high mortality, 4 deaths occurring in 34 cases.

In the gastrojejunal ulcers occurring after posterior gastroenterostomy and not complicated by hemorrhage, perforation, or fistula of the colon, the mortality was 6.5 per cent, 7 deaths in 108 cases. When an anastomosis of the Hofmeister-Finsterer type was used the mortality dropped to 5 per cent, 4 deaths in 82 cases, which is therefore only slightly higher than the mortality of the customary type of surgery, resection of the ulcer. (On the other hand, in the cases of gastrojejunal ulcer following resection, the mortality of radical operation was much higher, 5 deaths in 25 cases, or 20 per cent. Radical resection for recurrence of gastrojejunal ulcers had a mortality of 16.6 per cent, 2 deaths in 12 cases.)

Following *perforation* the results obtained were poor. Both patients operated upon died. Similarly unsatisfactory results were obtained in cases complicated by acute profuse hemorrhage. In cases of this type which were operated upon late there were 4 deaths in 5 cases, whereas in 4 others operated upon early, the results were good, as all 4 cases recovered.

Gastrojejunal-colon fistula had a high mortality, 17 patients were operated upon with 6 deaths, a mortality of 35.2 per cent. This mortality occurred not only when the colon was resected at the same time, as was done in 11 cases with 4 deaths, but also when the colon was separated and closed, which was done in 6 cases with 2 deaths.

The type of *anesthesia* has a marked influence upon the operative mortality. General anesthesia was used as little as

possible, being replaced by local anesthesia, either mesenteric or splanchnic. Of 176 cases operated upon under splanchnic anesthesia it was possible to operate on 130, 73.8 per cent, without ether supplementation. In the remaining cases ether was used before the splanchnic anesthesia to separate the adhesions, and only in 7 cases were more than 150 cc. of ether used. In these cases, there were no deaths from pulmonary inflammation even though 12 of the patients were from 60 to 78 years old. Two of the latter died, 1 from volvulus of the sigmoid and 1 from peritonitis.

The best permanent end results were obtained with extensive gastric resection and anastomosis of the Hofmeister-Finsterer type. Fifty cases were completely healed; in 5 the condition was markedly improved, and none presented failure. However, of 22 cases in which the modified Billroth I method of von Haberer was used only 18 were cured, in 1 the condition was markedly improved, and in 4 (13.6 per cent) it remained unimproved. The poorest results were obtained with the "Y" type of anastomosis, which was employed in 21 cases, of which only 7 were cured, in 1 the condition was improved, and in 13 (61.9 per cent) it remained unimproved. Of these 13 patients still having gastrojejunal ulcer, 6 were again operated upon after either hemorrhage or pain recurred. The "Y" type of anastomosis which was condemned by the author in 1924 has not been used in the last 13 years. In the "Y" type of anastomosis it is necessary to remove even more of the stomach in order to achieve permanent healing.

The author performed a radical operation with "Y" anastomosis for gastrojejunal ulcers which occurred after gastroenterostomy in 2 brothers in 1919, and

found it necessary to operate for recurrent gastrojejunal ulcer in 1921. At this time he left only one-fifth of the stomach and again established gastrointestinal continuity by a "Y" type of anastomosis. Both of the brothers have remained well now for 15½ years.

In 14 cases of recurrent gastrojejunal ulcer a "Y" type of anastomosis was performed 10 times, anterior gastroenterostomy with enteroanastomosis 3 times, and resection of the antrum once.

There were 8 cases in which from 3 to 7 operations had been done. These cases were described by Mandl as being "surgically incurable," but through a new resection and avoidance of the "Y" type of anastomosis, permanent healing was achieved.

Gastrojejunal ulcer should be prevented as far as possible by the avoidance of gastroenterostomy and by resection of at least two-thirds of the stomach so that only the normal cardiac third remains. The "Y" type of anastomosis as well as enteroanastomosis should be avoided not only in resection for ulcer, but also in resection for exclusion.

Antral Gastritis and Spasm

A discussion of gastritis and its roentgenologic interpretation is given by R. Golden.⁹⁹ The cause of the condition is unknown. It begins in and may be limited to the mucosa but frequently extends to the deeper layers. It has been pointed out that as far as the motility is concerned, the antrum is the most important part of the stomach and consequently inflammatory changes in this region may produce serious disturbances in gastric function. This condition has been termed "antral gastritis" and may produce any or all of the symptoms of peptic ulcer, such as pain, hemorrhage, and vomiting.

Diagnosis — The diagnosis depends mainly on gastroscopic and x-ray examination. Some writers have noted that in many cases there are no changes which can be demonstrated by the x-rays, but the author is convinced that certain cases may be recognized with the x-rays by a study of the changes in the gastric form and function.

Normally, as the narrow peristaltic wave enters the antral region, its relaxing edge decreases and its contracting edge increases in speed, in this way a portion of the lower end of the stomach is closed off. This results usually in expulsion of the gastric contents. Then the wall relaxes promptly and the lumen returns to its normal width and contour. This is known as "antral systole." The author's observations suggest that antral systole is associated with contraction of the longitudinal muscle toward the pylorus. In the normal stomach the mucous membrane is freely movable over the muscle. Forssell has demonstrated that the formation of mucosal folds is the result of the contraction of muscularis mucosae. In some cases the mucosal folds in the antrum run irregularly in a transverse direction, and when antral systole occurs they appear to change direction and run nearly parallel with the long axis of the stomach. For this change to take place there must be a movement of the mucous membrane in a cephalad direction which stretches it tightly beneath the muscular contractions. Failure of this mechanism may account for the occasional observation of herniation of the prepyloric mucosal folds through the pylorus.

Movement of the mucous membrane may be disturbed by inflammatory changes of the muscularis mucosae and the submucosa. Edema of the mucosa has been frequently noted. Changes about and within the ganglion cells may

interfere with the function of the mural nerve plexuses. In any event, the following disturbances in motility have been observed:

1. Peristalsis may be very irregular in depth and timing. The waves seem stiff and fail to develop into antral systoles.

2. Prepyloric narrowing due to spasm may be present

3. Pylorospasm may be present.

In addition there is frequently delay in emptying and there may be mucosal erosions.

There is evidence to indicate that gastritis is an important factor in the production of hypertrophy of the pyloric muscle. The most important x-ray sign in this condition is elongation of the pyloric channel with preservation of the mucosal folds.

Differential Diagnosis—The differential diagnosis of antral gastritis from *carcinoma* may be difficult. Pressure methods to demonstrate mucosal folds in the narrowed area are particularly helpful. Ordinarily the folds are obliterated by an infiltrating carcinoma. If atrophic changes are present the diagnosis becomes even more difficult. A palpable mass in the antral region favors the diagnosis of carcinoma. The writer has found atropine of little value in the study of these cases but recommends gastric lavage and repeated examination. If doubt persists, however, operation is advised.

Results of Gastrectomy

H. A. Dias¹⁰⁰ notes that gastrectomy is being employed more frequently; at first used only in gastric cancer, it is now employed in gastric and duodenal ulcer, because it effects a radical cure without the danger of postoperative jejunal ulcer.

However, when an extensive gastric resection is done with the removal of from two-thirds to four-fifths of the stomach and the duodenal bulb, it is not only the secretion of hydrochloric acid that is terminated. Other important secretions and functions are abolished. These include, in addition to pepsin and the lab ferment: (1) The antianemic hormone; (2) secretin, which is produced normally by the action of the gastric acid and stimulates pancreatic secretion; (3) cholecystokine, the hormone studied by Ivy, which acts upon the bile secretion; (4) enterogastrin, and (5) incretin or duodenin, which stimulates the internal secretion of the pancreas.

When gastric digestion is abolished and the production of these various hormones which affect the entire digestive processes is stopped, various intestinal disturbances may result. The absence of hydrochloric acid results in the increase of microorganisms in the upper intestines and favors the invasion of the upper intestines by colon bacilli.

However, the most important after-effect of gastrectomy is undoubtedly the *postoperative anemia*. Numerous cases of this type of anemia have been reported in recent literature. The anemia may be of 2 varieties—true (hyperchromic and megalocytic) pernicious anemia, and hypochromic microcytic anemia. The latter type occurs after a considerable percentage of gastrectomies, according to recent reports, and especially in women. In some cases it has been found that the hypochromic microcytic form of anemia tends to become hyperchromic and pernicious as it progresses. Achylia is as typical of this type of hypochromic anemia as it is of pernicious anemia, whether the achylia is the result of gastrectomy or is a non-surgical achylia.

Lack of iron due to deficient absorption and absence of the gastric anti-anemic factor are the chief causes of the anemia following gastric resection. Other factors, such as deficiency of vitamin B or an endocrine factor, are secondary. It is probable, as Morris has suggested, that if the iron deficiency predominates the anemia is hypochromic; if a deficiency of the antianemic factor predominates, the anemia is hyperchromic.

One case is reported in a woman who, after gastrectomy for a duodenal ulcer, developed symptoms of hypothyroidism and ovarian deficiency, and also an anemia with both macrocytosis and microcytosis and a color index of 0.99

The author is convinced that gastrectomy should not be employed as the routine treatment for peptic ulcer; its possible effects, and especially the danger of severe anemia, should receive more serious consideration

Form and Function of Stomach After Gastrectomy—A clinical and roentgenologic study of 52 patients subjected to a partial gastric resection has been made by M. P. Fedyushin.¹⁰¹ Roentgenologic observations were made from 1½ to 2 weeks after the operation and were repeated at intervals of from 2 months to 2 years. Forty-four of the patients were operated on for a malignant tumor and 8 for ulcer. With the exception of 1 case in which total extirpation was made and of 3 cases in which the continuity of the gastrointestinal tract after resection was re-established by the first Billroth operation, the operation performed was the Finsterer modification of the Reichel-Polya method in the remaining 48

The author concludes on the basis of his clinical observations that even a pronounced functional alteration as demonstrated by roentgenologic studies does not preclude a clinically satisfactory re-

sult. This fact is to be accredited not so much to the advantages of any method of resection but rather to the great adaptability of the gastrointestinal tract to the new conditions. Symptoms of a "small stomach" are due to insufficient adaptation and correction of the disturbed anatomic and physiologic relations, to errors in the method of resection and to such complications as perigastritis, gastritis and jejunitis.

The form of the remaining stomach shortly after the resection depends on the operative method, the inflammatory changes and the gastric tonus. With the lapse of time the form of the gastric stump alters under the influence of the pressure of its contents. The emptying of the stomach after resection is a complicated act in which hydrostatic pressure, the systole, the reflex closure of the anastomosis and the peristaltic movements of the afferent loop of the intestine are concerned. The predominant part in the emptying act is assumed in the early postoperative period by the hydrodynamic factor, while in the late period the gastric tonus and the peristaltic activity of the afferent loop of the intestine are the determining factors. The operative method determines the early form of the gastric stump and its later adaptability to the new functional demands.

The technical points in the resection which influence the proper emptying are: (1) The creation of a sufficiently wide anastomotic stoma, not however to exceed that of the lumen of the afferent loop of the intestine in order to prevent retrograde spilling; (2) placing of the stoma so that it occupies the lower segment of the right border of the stump after the latter's usual shift to the left; (3) avoidance of the formation of the spur in anastomosing the ends of the gastric stump and the intestine, and (4) turning in of the angle of the lesser

curvature into the interior of the stomach in order to avoid retrograde evacuation.

Complications After Resection of Stomach—The main cause of early and late complications after resection of the stomach and gastroenterostomy, such as gastric hemorrhage, separation of the sutures of the stump, subdiaphragmatic abscess, subperitoneal phlegmons and marginal ulcers, appears to be the method of using clamps. L. V. Serebrenikov and V. P. Snezhkov¹⁰² carried out 32 experiments on 10 dogs. Clamps were applied on the antral part of the stomach in 15 experiments in the first series and on the jejunum in 16 experiments of the second series. The Doyen and Linnartz types of clamps were employed. These were applied for from 25 to 45 minutes, locked on the third indentation of the lock. Sections of tissue were taken immediately after removal of the clamps and 20 minutes after the stomach wall appeared to be recovered. A study of the macroscopic and microscopic picture of the stomach and intestinal walls was carried out after the removal of the clamps. Altogether 124 pathologic preparations were examined.

The changes found were as follows: Severe traumatization of all layers of the stomach and intestinal walls, especially of the mucosa, which appeared completely crushed, a considerable amount of extravasation was observed at a considerable distance from the lesion, displacement of the various layers of the wall of the stomach with relation to each other, with formation of cavities filled with blood and thrombosis and necrosis of the vessels of the stomach and intestinal walls and of the vessels of the omentum and mesentery, was observed. The authors estimated that the extent of pressure exerted by the Doyen clamps equaled 9 kg. for each centimeter of surface of the branches and that by

the Linnartz clamps was 17 kg. On the basis of their experimental data the authors recommend, in cases of resections for cancer of the stomach in which the employment of clamps is unavoidable, the use of the Spasokukotzky type, exerting less pressure, and in cases of ulcer an operative procedure in which no clamps are employed.

Carcinoma of the Stomach

Etiology—The theories concerning the cause of carcinoma of the stomach have been elaborated by J. Morley.¹⁰³ He points out that 82 per cent of chronic ulcers of the stomach but only 13 per cent of gastric carcinomas occur in the middle two-thirds of the lesser curvature. On the other hand, only 12 per cent of chronic ulcers occur in the prepyloric region, while 66 per cent of the gastric carcinomas occur in that region. This is given as evidence against the contention that carcinoma is secondary to chronic ulcer. Furthermore, the average duration of symptoms in the author's series of cases of carcinoma was 127 months, as compared to 103 years in cases of ulcer. It is not denied that malignant transformation in an ulcer may occur, but it is less frequent than is often stated. The author does not hold to Hurst's view that chronic gastritis is a common predisposing cause of carcinoma.

Carcinoma of the stomach is classified according to location: (1) Carcinoma of the cardiac end of the stomach; (2) carcinoma of the body of the stomach, and (3) pyloric and prepyloric carcinoma. The symptoms depend to a great extent on the location of the lesion.

Symptoms—The earliest symptoms of carcinoma of the stomach usually are a vague discomfort after meals and an unaccountable failure of appetite. The patient is usually over 40 years of age

and has not suffered from indigestion before. With the failure of appetite there is a steady loss of weight and, as a rule, a progressive development of anemia.

In carcinoma of the cardiac end of the stomach, there is commonly an early onset of dysphagia due to stenosis of the cardiac orifice. Only a roentgenological examination will differentiate this condition from carcinoma of the lower end of the esophagus.

Obstruction is most unusual in lesions of the body of the stomach. In some patients loss of appetite may be the only early symptom. Other patients may have a feeling of flatulent distention of the stomach and eructation of gas with an offensive odor. Anemia and weakness are progressive, as well as loss of weight. X-ray examination reveals the lesion or confirms the diagnosis.

Lesions of the pyloric end of the stomach are most common and most hopeful. They are hopeful because the obstruction often occurs early and the growth is accessible for surgical removal. In the presence of stenosis pain is the most marked feature. Visible peristaltic waves may be seen in some patients. A palpable mobile tumor is not a contraindication to surgery in the opinion of the author.

Late symptoms are secondary deposits of tumor in the liver and peritoneum. In each sex the pouch of Douglas should be examined for hard secondary tumors. In the female a pelvic examination may reveal large secondary ovarian masses known as Krukenberg tumors. Jaundice and ascites are very late symptoms of metastases.

Differential Diagnosis—The differential diagnosis may at times be difficult. In pernicious anemia the distress after taking food is slight or absent and rapid loss of weight is rare. Examination of

the blood and x-ray studies will confirm the diagnosis.

Simple peptic ulcer may simulate a carcinoma of the stomach, and *vice versa*. If x-ray examination shows the lesion on the duodenal side of the pylorus, then the presence of an ulcer is assumed. Failure to heal after adequate treatment for about 3 weeks and the persistence of blood in the stool justify surgical interference.

Occurrence of Ulcer Carcinoma and Carcinoma in the Stomach with Ulcer—Material studied by H. B. Wulff¹⁰⁴ was comprised of 609 confirmed cases of gastric carcinoma treated at the Surgical Clinic of Lund from 1924 to 1933. It was divided into 2 groups.

The first group consisted of 489 cases of gastric carcinoma in which there were no symptoms or findings suggestive of an ulcer prior to the development of the gastric carcinoma. In this series the history of symptoms ranged from no symptoms to symptoms over a period of 3 months for 26.7 per cent, from 3 to 6 months for 29.3 per cent, from 6 to 12 months for 27.3 per cent and for more than 12 months for 16.7 per cent. The presence of a previous ulcer in this group was not considered by the essayist.

In the next group of 120 patients the history, physical findings, or laboratory work suggested a previous ulcer. Sixty-nine of these 120 patients had longstanding digestive disturbances, but the picture was not typical enough so that an absolute diagnosis of gastric ulcer could be made. In the remaining 51 patients the findings were so characteristic that an ulcer diagnosis could be made with assurance. Twenty-eight of the latter 51 had characteristic pain occurring in the proper area and with the proper periodicity. Twenty-one of the 51 showed, in addition to typical ulcer pain, such characteristics of ulcer as hemor-

rhage, perforation, and niche formation. Eight of these 21 had ulcer hemorrhage over a period varying from 2 to 30 years prior to the diagnosis of carcinoma. It was therefore possible to make a diagnosis of previous ulceration in 51 of 609 patients with gastric carcinoma, or in at least 8.3 per cent of the cases of gastric carcinoma treated in the Lund Clinic from 1924 to 1933, a previous diagnosis of either gastric or duodenal ulcer could be made.

It was of further interest to know that in 1911 Petrenee collected from the same hospital 199 definite cases of gastric carcinoma which were treated from the years 1898 to 1908, and concluded that at least 8.5 per cent of the gastric carcinomas had been preceded by gastric ulcer. Carcinoma probably had an ulcer basis in 2.1 per cent of the cases. In 1.5 per cent this diagnosis of carcinomatous ulcer could be made and based upon histopathological examination. In 0.8 per cent the diagnosis could be verified by roentgen examination because an ulcer had been demonstrated previously at the site of the carcinoma, and in 0.2 per cent the diagnosis could be made both histopathologically and roentgenologically.

Gastric Acidity in Carcinoma of the Stomach. Observations on gastric acidity before and after development of carcinoma of the stomach has been made by M. W. Comfort, W. L. Butsch and S. B. Fusterman¹⁰⁵ in 79 patients of all ages. The gastric secretory activity of the 79 patients destined to develop cancer of the stomach was below normal before the development of cancer. After an interval of years averaging 6, and after each patient had acquired cancer of the stomach, the percentage of achlorhydria had increased from 38 to 64.6 per cent, while the mean concentration of free hydrochloric acid in the gastric con-

tents of the remaining 28 patients who retained free acid was changed but slightly. The depression of gastric acidity in patients destined to have carcinoma of the stomach is a progressive and selective process, appearing early in life and at all ages. The low secretory activity of the stomachs of patients with gastric cancer is present, for the most part, before the development of cancer. The loss of gastric acidity occurred in patients both with high and with low concentrations of free acid, but more frequently in cases in which the concentration of acid was low before the development of cancer. A further reduction of gastric acidity occurs after the development of cancer. Theoretically, the low secretory activity of persons destined to have carcinoma of the stomach may be present at birth (a developmental defect in the secretory mechanism) or it may occur after birth as the result of an abiotrophy of the acid-secreting cells or as the result of inflammatory destruction of the gastric mucous membrane. The loss of gastric acidity in adult life excludes a developmental defect as the cause of the loss in a considerable number of cases, while the presence of marked, diffuse atrophic gastritis in almost all cases of achlorhydria and the absence of a marked diffuse atrophic gastritis in almost all cases in which there is free hydrochloric acid in the gastric contents greatly favor chronic atrophic gastritis as the important cause. Chronic gastritis, as well as the tumor itself by its local and systemic effects, may be responsible for the depression of gastric secretion after the development of gastric cancer.

Treatment—Total Gastrectomy for Carcinoma of Stomach.—During the decade from 1926 to 1936, 713 patients with carcinoma of the stomach were admitted to the Massachusetts General

Hospital, Boston. According to A. W. Allen¹⁰⁶ the majority of these were deemed inoperable after physical examination and roentgen-ray studies, and some after peritoneoscopy.

A considerable number were offered exploration but refused it; 160 patients were subjected to exploration only be-

the cut edge of the stomach turned in so as to leave the disease excluded. The mortality in the palliative group was 35 per cent.

In 176 cases, partial gastrectomy was done. These operations included all partial resections from excision of the antrum to subtotal gastrectomy. In a few

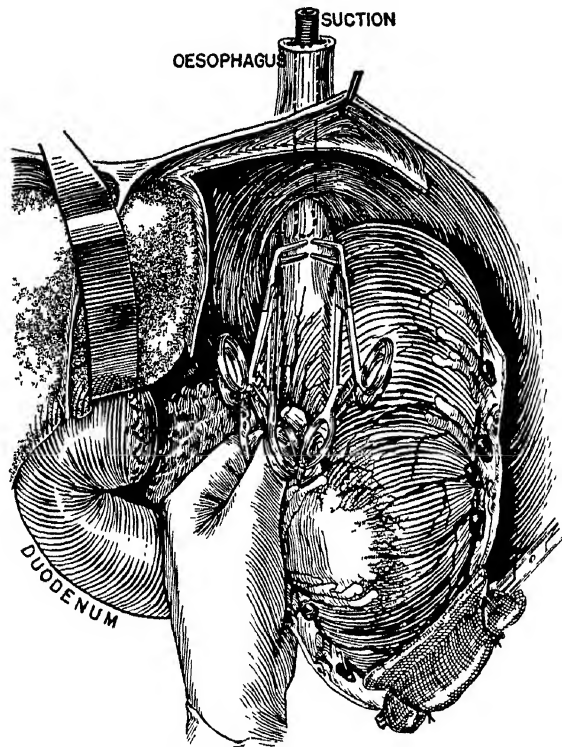


Fig. 64—Schematic drawing illustrating the exposure of the lower end of the esophagus. Note that Levine tube has been withdrawn from the stomach sufficiently to allow the tip to rest in the lower esophagus. The left lobe of the liver has been detached from the diaphragm and held out of the way by a flat retractor. (Courtesy of *Am. J. Surg.* 39: 35, 1938.)

cause studies failed to reveal positive evidence of their unamenable condition. Thirty (18 per cent of these) succumbed before convalescence had progressed sufficiently for their discharge.

One hundred and five of the 713 had palliative operations, the majority of these being gastroenterostomy. However, a considerable number had transections of the stomach proximal to a fixed growth and a posterior Polya anastomosis with the distal segment of

an involved segment of transverse colon or pancreas was included in the resection. The mortality in this group was 33 per cent. End results will be published on the survivors by Parsons and Welch.

In this past decade, 16 total gastrectomies have been done in this hospital; 5 patients were operated upon by the author, and in the remaining 11 cases 8 other members of the surgical staff participated. Fourteen of the patients had

cancer of the stomach, 1 had lymphoblastoma superimposed on an old ulcer for which gastroenterostomy had been done previously, and the remaining patient had a large benign ulcer that was

time of this report, but 2 of them are believed to have had recurrences 9 months and 3 years, respectively, after operation. Two are believed to be free of recurrence 14 months and 4½ years,

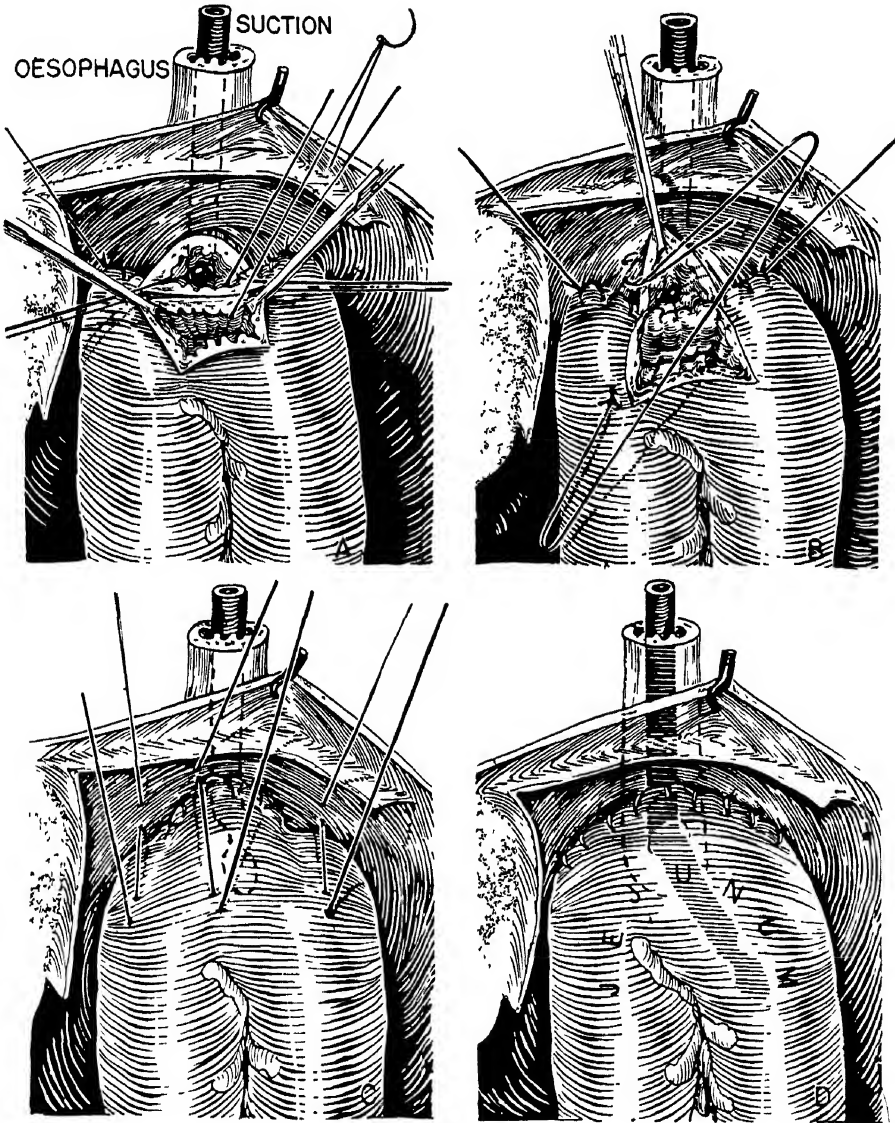


Fig. 65—Schematic drawings A and B, illustrating a careful approximation of the open end of the esophagus to all layers of the jejunum. The sutures are carried completely around the stoma inverting the mucous edges. C and D, the anterior wall of the jejunum is approximated to the diaphragm, completing the original circle of fixation sutures. (Am J Surg 39:35, 1938.)

thought to be cancer at the time of operation. Eight, or exactly half, of the patients survived the operation and left the hospital in a comfortable state of health. Five are still living at the

respectively, after operation. The patient who had an ulcer is thought to be well although she cannot be traced at this time. The patient living the longest time so far had a highly malignant adeno-

carcinoma with metastases to the regional lymph nodes

An analysis of the operative technic employed on these cases, a study of the literature, and various suggestions that seem applicable have brought about a possible standardization of the operative technic for total gastrectomy, which the author believes may be carried out in

ner described in detail below with only 2 operative deaths. One death occurred from peritonitis and pulmonary infection and the other from lobar pneumonia 7 days after operation. In the latter case there was involvement of the transverse colon and pancreas which necessitated the removal of the whole stomach, a section of the transverse colon, the

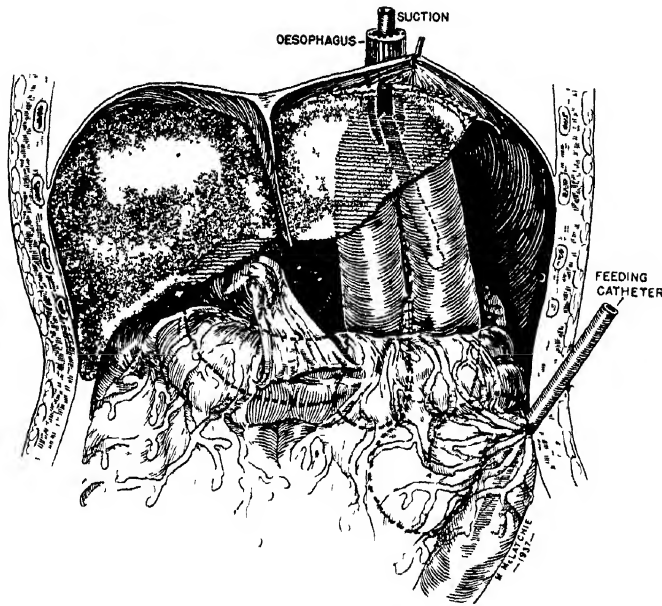


Fig. 66—Schematic drawing illustrating the Levine tube brought down through the esophagojejunostomy stoma into the distal limb of jejunum. The left lobe of the liver has been reattached to the diaphragm. An enterocenterostomy has been made at a low level between the jejunal limbs. A jejunostomy for feeding has been established. (Am. J. Surg. 39:35, 1938.)

suitable cases with a reasonable expectation of immediate success. It seems likely that an occasional 5-year cure may be obtained, and in all cases the author has had the satisfaction of having offered these otherwise hopeless individuals a comfortable respite that is worth while.

The type of anastomosis in relation to the mortality in this group is suggestive. Three patients had esophagoduodenostomy and all died. The tendency of such a suture to separate and produce a fatal peritonitis was recognized by Finney and Reinhoff. Eight patients were operated upon in the man-

spleen, and two-thirds of the pancreas *en bloc*. A detailed report of this case record has been made.

Operative Technic Figures 64 to 66 illustrate the method which the author believes at present to be a logical procedure. He thinks the patient will withstand operation better if he is kept in the hospital several days for rest and the establishment of a fluid and salt balance. During this time, **blood transfusions, glucose, and cevitic acid** are administered. With the patient at his best, the operation is planned so that time is no factor.

The *anesthesia* can be local to the abdominal wall with splanchnic block, usually supplemented with nitrous oxide, oxygen, and ether in a closed machine. A well-given intratracheal anesthesia of the above mixture is ideal from the surgeon's standpoint, and in certain types of patients, particularly those with deep anteroposterior proportions, it may be best to use this from the onset. A Levine tube is introduced into the stomach before the anesthesia is started.

Postoperatively, the feeding should be put into the jejunostomy catheter for 2 weeks. This is done best with a continuous drip apparatus which should be regulated in such a manner that distention is reduced to a minimum. Normal salt solution or sterile water is used for the first 48 hours, then broth, dilute milk, and egg albumin are added. As soon as the patient is eliminating gas freely any liquid food can be used.

Stomatitis and diarrhea have complicated the convalescence in some of these cases. The author believes they can be eliminated by the administration of cevitic acid before and after operation with regulation of the type of food introduced through the jejunostomy. High caloric mixtures should be avoided in the early feedings and non-gas-producing liquids used. In one instance, the author thought that the addition of dilute hydrochloric acid to the feedings helped to control the diarrhea. The patient is allowed a small amount of water by mouth after the third day. Feedings are begun and well established by this route before the jejunostomy tube is removed. The patient should be discharged on a well-balanced diet and should be urged to eat finely chopped meat and liver. It is surprising to see them gradually extend the time interval between feedings and augment their ability to increase the amount of food taken at 1 time without distress.

The patient in this series who has survived the longest number of years eats 3 substantial meals a day with only occasional feedings in between. He has maintained his normal weight, blood picture, and works regularly. He complains a bit about having to take most of his food in a finely divided form and gets some discomfort if he eats too rapidly.

Alcoholization for Alleviation of Pain in Gastric Cancer and Gastric Ulcer—The method of G. U. Perelman¹⁰⁷ is based on the fact that alcoholization causes a break in the nervous tissue. From 15 to 20 cc of an 80 per cent solution of alcohol was used for this purpose. In order to effect a break in the neurofibers of the sympathetic, passing through the stomach and alleviation of the pain in cases of inoperable cancer or gastric ulcer, injections should be made into the lesser omentum or, if the usual technic is to be employed, a splanchnic anesthesia is to be induced. The author reports 22 cases of alcoholization: in 10 splanchnic anesthesia was carried out, in 10 injections of alcohol were given in the lesser omentum and in 2 combined injections were given. The result of alcoholization was favorable, since it caused cessation of pain for from 1½ to 6½ months in cases of inoperable cancer. In cases of callous ulcer penetrating into the neighboring organs and in cases of pain in organs not innervated by the gastric nerve (liver), no effect is accomplished by this method. It may even cause an increase of pain, since injections of alcohol increase inflammatory adhesions.

Nutritional Disturbances Associated With Diseases of the Stomach and Duodenum

The altered physiology and biochemistry associated with lesions of the stomach and duodenum are as important

as the etiology, symptoms, pathology, and operative correction of the condition. W. G. Maddock¹⁰⁸ states that nutritional disturbances may cause vitamin, mineral, protein, carbohydrate, or fat deficiencies, either individually or in combination. Caloric requirements cannot always be met adequately, although the parenteral administration of glucose is a distinct aid in the prevention of ketosis. However, the substances that can be administered in quantities by the intravenous route, namely, water, glucose, and sodium chloride, are inadequate to maintain the health of the patient for more than 2 or 3 weeks. Vitamins and proteins are also needed, and these requirements are often a considerable problem in the cases of patients who are seriously ill. Many of them have had a pre-operative period of malnutrition for months, and a long-standing deficiency is present. The purpose of this study is to review briefly the vitamin and protein deficiencies as they may affect the surgical patient with lesions of the stomach and duodenum.

Vitamin A deficiency has been reported in patients with diarrhea secondary to gastrocolic fistula. Such a deficiency may be determined by the "keratinization test" of Blackfan and Wolbach, in which conjunctival scrapings show abnormal cornified epithelial cells. Carotene and fish oils meet this deficiency.

Vitamin B deficiency occurs in patients with pyloric stenosis, gastric carcinoma, and polyps, it may occur secondarily in patients upon whom gastroenterostomy has been performed, and may follow persistent vomiting after surgery on the biliary tract. It can readily be corrected by the administration of vitamins B₁ and B₂.

The early signs of vitamin C deficiency may be determined from the urinary

excretion, body store, and blood plasma, or from serum concentrations of ce-vitamic acid. A promising test consists in the production of venous stasis in an arm for 15 minutes with a blood-pressure cuff at 50 mm. of mercury, and then the counting of the number of petechial hemorrhages in a skin area of 60 mm in diameter in the antecubital fossa. The test is positive in the presence of more than 8 petechiae, 5 or fewer constitute a negative reaction.

Vitamin D deficiency may occur with celiac disease, sprue, external biliary fistula, and chronic jaundice. The value of viosterol in decreasing the hemorrhagic tendency in patients has been demonstrated by many investigators.

In the absence of gross bleeding, patients with gastric or duodenal ulcers usually show little change from the normal. On the other hand, patients with gastric carcinoma show a secondary anemia due to continual oozing from the carcinomatous surface. Pernicious anemias have followed partial resection for carcinoma, ulcer, and syphilis of the stomach, as well as gastroenterostomy for peptic ulcer. The treatment varies with the type of anemia. The secondary anemias respond well to large doses of iron. For pernicious and other forms of hyperchromatic anemia large doses of liver are indicated.

The effects of protein deficiency are more frequently seen in surgical patients with malnutrition from disturbed gastrointestinal function than in patients with malnutrition due to vitamin deficiencies. Prolonged low protein ingestion results in low plasma proteins, and nutritional edema is a rather common sequel. The edema may, however, be secondary to profuse surgical drainage, sepsis, loss of serum protein by massive hemorrhage, retention of base due to disturbed renal function, and the administration of ex-

cessive amounts of water and salt. This water retention is of major significance because patients who are seriously ill and present malnutrition or sepsis have been shown to develop retention routinely if the water requirements supplied intravenously in the form of saline solution and sodium chloride were not needed. Jones and Eaton have shown that this retention may occur even when serum protein levels are approximately normal. Many investigators have shown clinically and experimentally that in the presence of low serum proteins the salt is essential for edema. The first thought of the surgeon, on finding edema in the sick surgical patient who has been receiving fluids parenterally, should be: "What are the serum protein values and how much sodium chloride has been given?" It is unnecessary and even

harmful to the sick patient to administer more than a few grams of the sodium chloride daily when the plasma chlorides and carbon-dioxide combining power are normal, and when no abnormal loss of sodium chloride is occurring. Five per cent glucose in water may be used as it rarely produces edema.

As a prophylactic measure in patients with long-standing, severe malnutrition, several transfusions prior to the operation, and the passage of a Jutte tube down through the gastroenterostomy stoma to the distal jejunum, during the operation, have been advised. This procedure permits nourishment early in the postoperative period. Eggs and milk may be utilized as a source of protein, and yeast and cod-liver oil will supply essential vitamins until the patient can tolerate solid foods.

APPENDICITIS

By FREDERICK A. FISKE, M.D.

The Appendicitis Problem—In an editorial, Reid¹⁰⁹ points out the difficulty in making a diagnosis of the atypical cases of acute appendicitis. He gives a clinical picture of the acute pelvic appendix and the acute retrocecal appendix which may mislead the most sincere diagnostician. It is his feeling that the conservative treatment of cases of peritonitis and appendiceal abscess is being misinterpreted by the laymen and doctors alike; and this treatment will be a factor in increasing the mortality rather than decreasing it unless it is properly regulated. The fact that it has served as an excuse for home treatment by some doctors is enough to condemn it.

"The whole-hearted support of educational campaigns in the press, in paid

advertisements, in our public schools, and through radio programs and lectures would indicate an unanimous agreement among the medical profession regarding the advisability of early operation for acute unruptured appendicitis, yet there are doctors among us who do not follow this policy. Should organized medicine continue by its silence to recognize that, after all, their opinion may be right, that in this problem of appendicitis they are a law unto themselves, and that no matter what happens they are to be protected by a strict code of medical ethics?

"When will organized medicine assume some responsibility for censuring those doctors who refuse to obey them? Until it does, the public will continue to pay the price of an unnecessarily high

TABLE I

CLASSIFICATION OF PATHOLOGIC CONDITIONS OF APPENDICES, WITH THE INCIDENCE AND MORTALITY FOR EACH GROUP

Condition in Appendix	Number of Appendices	Percentage*	Number of Deaths	Mortality Percentage
No Microscopic Examination	161		1	0.62
Mucocoele	3	0.16	0	0.00
Tuberculosis	5	0.26	1	20.00
Tumor	6	0.32	0	0.00
No Inflammation	702	36.9	5	0.71
Normal	629	33.1	4	0.62
Atrophic	73	3.8	1	1.37
Inflammation	1188	62.4	20	1.67
Simple Chronic Appendicitis	573	30.1	10	1.75
Marked Inflammatory Changes	615	32.3	10	1.63
Chronic Catarrhal Appendicitis	82	4.3	1	1.22
Chronic Exudative Appendicitis	157	8.3	2	1.27
Acute Appendicitis	33	1.7	0	0.00
Chronic Obliterative Appendicitis with Infiltration	106	5.6	1	0.94
Chronic Obliterative Appendicitis without Infiltration	183	9.6	4	2.19
Chronic Periappendicitis	31	1.6	0	0.00
Acute Periappendicitis	23	1.2	2	8.70
<hr/> Total	2065	100.00	27	1.31

*The percentages are calculated only on the 1904 appendices examined microscopically (Courtesy, Arch. Surg., Oct., 1937.)

death rate while professional ethics effectively defend the offenders in our own profession."

Pathology--In a histological study of 937 appendices removed at operation, Sappington and Horneff¹¹⁰ found acute appendicitis in 277 (29.5 per cent), subacute appendicitis in 43 (4.6 per cent), chronic appendicitis in 18 (1.9 per cent), appendicitis obliterans in 34 (3.7 per cent), and normal appendices 565 (60.3 per cent). This study did not include 300 appendices removed incidentally during a laparotomy for some other cause. They state that Aschoff found normal appendices in 35 per cent of 847 cases diagnosed and operated upon as examples of appendicitis. The statistics of Reid, Hobler, and Finney are criticized because no mention of normal appendix was made. The authors feel certain that some of these cases were normal from a histologic standpoint. They quote Finney as saying "it would

seem to us much better to remove half a dozen relatively normal appendices by emergency operations than to be responsible for the consequences which may attend waiting too long on one."

Shelley¹¹¹ reported the pathological findings in the appendices of 2065 consecutive cases in which the appendix was removed incidentally. The calculations are based on 1904 which were examined microscopically. The incidence and mortality for each type of pathological condition is tabulated (Table I). In 37 per cent of the appendices there was no evidence of inflammation, on the other hand, 62 per cent showed definite inflammation, 2 per cent of these were acute. Pathological conditions, other than inflammations of the appendix, found in this study were Oxyuris a lumen, 3 cases (0.16 per cent), mucocoele, 3 cases (0.16 per cent), tuberculosis, 5 cases (0.26 per cent); diverticulum, 1 case (0.05 per cent), hyperplasia of the mucosa, 3 cases (0.16

per cent), tumors, 6 cases (0.32 per cent). The tumors found were: Endometrial rests, 4 cases; carcinoid, 1, papillary adenoma, possibly malignant, 1.

In a study of 143 cases, presenting a typical history and physical findings of acute appendicitis, which at operation were found to have an apparently normal appendix and no other intra-abdominal pathology to explain the symptoms, and in which the pathologist found no gross or microscopic evidence of inflammation, Rea and Kleinsasser¹¹² were able to follow up 102 cases. Of these, 90 were well, and 12 suffered from the same or other symptoms. Of 73 patients who had been operated upon 4 or more years previously, 41 were followed; 32 (78.1 per cent) were well and 9 (21.9 per cent) were not. From this study of end results the authors feel that a surgeon need not feel apologetic over the removal of an appendix inactive from the viewpoint of the pathologist. It seems probable that many patients recover from appendicular colic and fail to exhibit microscopic evidence of inflammation of the appendix.

The appendicular mesentery shows microscopic lesions which vary with the form of appendicitis and are proportional to the intensity of the disease, according to the histological studies of Beluffi.¹¹³ He examined 245 appendices and their mesenteries removed surgically for acute and chronic appendicitis. In the acute cases, the mesentery showed edema, exudation, cellular infiltration, lymphangitis, rapid mobilization of the reticuloendothelial cells and perivascular infiltration, alterations in circulation, venous thrombosis, and suppurative thrombophlebitis occurred in grave cases. After regression of the acute phase, structural changes such as retraction, adhesions, thickening of the connective tissue and vascular walls, and lymphatic

infiltration are found in the mesentery. These changes are permanent. Their presence induces mechanical and functional disorders leading to stasis and future attacks of an acute nature. It seems possible that infection may be transmitted through the mesentery to distant abdominal viscera even after appendectomy, therefore ample removal of the mesentery is advocated.

Lawen¹¹⁴ states that the microscopic features of the entity he described in 1914 under the name of fibroplastic appendicitis are identical with those of terminal ileitis described in 1932 by Coohn, Ginzberg, and Oppenheimer. In his original description he states that fibroplastic appendicitis may involve the cecal wall, and the terminal ileum, and thus lead to a secondary terminal ileitis. He concludes that the tumor forming chronic stenosing ulcerative or nonulcerative terminal ileitis, and fibroplastic appendicitis and the analogous disorders of the ascending colon present an identical microscopic picture. The inflammation is the same type with different localization. In a number of cases the relationship between terminal ileitis and the inflammation of the appendix cannot be demonstrated. There are cases of ileitis in which it is possible to establish the etiologic relationship to an acute appendicitis and a chronic terminal ileitis which developed later.

Tumors—*Argentaffine Tumors*—According to Wyatt,¹¹⁵ these tumors have been reported to arise from all parts of the gastrointestinal tract except the esophagus, duodenum and rectum. In the small intestine the tumor is most frequently found at operation, while in the large bowel it is most frequent at autopsy. In the appendix it is most frequently associated with acute or chronic inflammation. The tumor itself is not always apparent on gross examination

of the appendix, and frequently the diagnosis is made only after study of several sections.

At present it is generally conceded that "carcinoid" or argentaffine tumors arise from Kultschitsky cells found in the base of the crypts of Lieberkuehn. Serial sections have shown that the tumor arises from the cells in the crypts, and that the cells both of the primary tumor and its metastasis contain silver reducing granules in their basal portions as do the Kultschitsky cells of the basal intestinal epithelium. On this basis the tumor should be classified as a true carcinoma.

The author reports 2 cases of argentaffine tumor of the appendix together with 1 case of multicentric argentaffine tumor of the cecum with metastasis to the liver. All carcinoids are slow growing malignant tumors, but they offer a good prognosis after surgical intervention; even when metastasis to regional lymph nodes has occurred.

From a series of 4224 appendices examined, Gnassi¹¹⁶ found 5 cases of carcinoid tumor. He reports the cases with reference to the clinical behavior and ultimate course.

Collins,¹¹⁷ *et al*, reported an interesting case of ulcerating carcinoid occurring in a Meckel's diverticulum. The signs and symptoms simulated a chronic peptic ulcer. They tabulated the data collected on 4 similar cases, 3 of them being found at autopsy and the other at operation which was fatal in 2 days. Their case is living after resection of the diverticulum.

Neuromata—A case of ganglioneuroma of the vermiform appendix in an 8-year-old colored girl was reported by Lichtenstein and Ragins.¹¹⁸ The tumor consisted of ganglion and Schwann cells and was confined to the mucosal layer. The tumor was a soft node measuring 4 by 2 mm, attached to the mucosa of the

distal third of the appendix by a pedicle 4 mm. in diameter.

Like ganglioneuroma in other parts of the body, this tumor is believed to have arisen from the differentiation of misplaced multipotential embryonal neurocytes. The malignant immature forms of neuroma occur almost exclusively in children, and the ganglioneuroma likewise appears early in life, but because of its benign character may be asymptomatic for a long time.

Fein,¹¹⁹ *et al*, reports the case of a male aged 65 years who had 3 attacks of acute abdominal pain over a period of 10 months. He was operated upon during the last attack and an acute diffuse appendix which showed a plexiform neuroma was removed. Convalescence uneventful. The tumor had broken through the muscularis mucosae and appears in the subserosa.

In serial section studies of 600 appendices using special stains of which Masson's trichrome was the most satisfactory, Fein, *et al*, found neuromata in 202 cases. Of these, 140 (69.3 per cent) were in the obliterative type and 82 (39.6) were nonobliterative (12 per cent acute suppurative, 26.8 per cent subacute—the rest chronic). The authors feel that neuromata are not unusual in the appendix and their presence is, possibly, the cause for removal of a large number of so-called "chronic appendices."

Diverticula—Diverticula of the appendix have never received the recognition accorded other diverticula of hollow organs. To support the view that they are not as infrequent as it is supposed, Wolff¹²⁰ quotes Stout as saying that when diverticula were specifically looked for in a large New York Hospital, 5 examples were found in 1 year while records of the previous 10 years failed to reveal a single case. Wolff gathered 33 cases in a 3-year period from 1663

cases of surgically removed appendices, whereas not a single case had been found previously. Multiple section method must be used, searching especially on the mesenteric and antimesenteric surfaces where they are most frequently found. Gross recognition on fresh specimens is extremely difficult. The specimens are best fixed for 24 hours. In this series perforation of the appendix had occurred at the diverticulum in 6 cases. The author feels that many perforations occur in the thin wall diverticula in which inflammatory changes have completely destroyed the evidence of diverticula.

He divides the diverticula of the appendix into 2 types. Congenital, which are very rare and all layers of the appendix are present in their normal proportion, and acquired, which are subdivided according to cause into *pulsion* and *traction* types. In his series only 1 case of the traction variety was encountered, the wall of a tuberculous abscess was adherent to the proximal portion of the appendix and several diverticula were present at the point of adhesion. The pulsion type was caused by increased intraluminal pressure forcing the mucosa and submucosa through a weakness of the muscle wall. Weak points are normally present along the mesenteric surface and to a lesser extent along the antimesenteric border, where the vessels from the subserous layer ramify into the submucosa. Most diverticula do occur in the region of this opening, the so-called hiatus muscularis.

Wunder¹²¹ describes the appendix removed from a man, aged 39, who had for some time vague pains in the abdomen, gradually localizing in the right hypogastric region. He was symptom-free 6 months after operation. The appendix disclosed intramural as well as external false diverticula, there was also chronic inflammation with scar formation

in the musculature, in addition the musculature was interspersed with nodules of connective and fatty tissue. Due to the inflammatory changes, the congenital character could not be determined.

When operating upon a man, 52 years of age, who had lower abdominal pain of 2 days' duration associated with nausea, Obenour¹²² found a gangrenous diverticulum of the colon lateral to the anterior tenia at the junction of the cecum and ascending colon. The mass extended laterally and was imbedded in the wall; it was 1 inch in depth and $\frac{5}{8}$ inch in diameter. All walls were involved and the lumen contained a fecalith $\frac{1}{2}$ inch in diameter. The appendix was suppurative. Recovery followed.

Mucocele—Mucocele are cystic dilations of the appendix due to proximal obstruction. They are of clinical importance, due to their potential malignancy, as manifested by the development of pseudomyxoma peritonei following their rupture. Waugh and Findley¹²³ describe the case of a woman, aged 49, with a mucocele of the appendix in which cancerous transformation, rupture, and diffuse pelvic transplantations had occurred. They feel that mucocele should be distinguished from simple hydrops of the appendix on the basis of histology. In simple hydrops due to proximal obstruction and accumulation of secretions the wall is thinned and the mucosal cells rendered atrophic, while in the true mucocele normal mucosa has been transformed into hyperplastic and even papillary types and the walls are thickened.

A mucocele of the appendix measuring $9\frac{1}{2}$ by 3 cm was reported by Craig and Fortner¹²⁴. It was removed from a woman, aged 33, who also had a left ovarian cyst removed. A satisfactory recovery followed.

According to Jirka and Scuderi,¹²⁵ the post-mortem records of Cook County

TABLE II

SHOWING THE NUMBER OF SPECIES OF AEROBIC MICROORGANISMS FOUND AND THEIR PREVALENCE

Microorganism	No of Cases
1. <i>B. coli</i>	79
2. Nonhemolytic Streptococcus	26
3. Diphtheroid Bacillus	26
4. <i>B. lactis aerogenes</i>	26
5. Green Producing Streptococcus	9
6. <i>Streptococcus hemolyticus</i>	9
7. <i>Micrococcus tetragenes</i>	8
8. <i>Sarcina</i>	8
9. <i>Staphylococcus</i>	6
10. <i>B. pyocyaneus</i>	5
11. <i>B. proteus</i>	5
12. <i>B. subtilis</i>	5
13. <i>B. mesentericus</i>	3
14. <i>B. fecalis alkaliogenes</i>	3
15. <i>B. influenzae</i>	1
16. Yeast	1
Negative Culture	1

(Courtesy, Annals of Surgery, April, 1938)

Hospital from January, 1929, to January, 1937 (9180 cases) revealed only 4 instances of mucocele, or 0.043 per cent. From July, 1928, to January, 1937, among 9535 surgically removed appendices there were 22 (0.23 per cent) instances of mucocele. The reports of other investigators give an incidence of 0.2 to 0.68 per cent.

Bacteriology—In a bacteriological study of 100 cases of acute perforated appendicitis with abscess, local or general peritonitis, Altmeier¹²⁶ found a complicated bacterial flora composed of various microorganisms which have been isolated from the intestinal tract of man. As seen from Table II the most frequent aerobe was the *B. coli*. A pure culture of aerobes was obtained in 24 instances, of 2 aerobes in 63, of 3 aerobes in 10, of 4 aerobes in 2. The most frequent combination of aerobes was *B. coli* and streptococcus nonhemolyticus. In 96 of the 100 cases studied, anaerobic organisms were found, the organisms thus cultivated are shown in Table III. *B. melano-*

TABLE III

SHOWING RESULTS OF THE ANAEROBIC CULTIVATION OF THE PERITONEAL EXUDATE

Species of Anaerobic Bacteria	No of Positive Cases	Percentage of Total Cultures
1. <i>B. melanogenicum</i>	89	92.7
2. Nonhemolytic Streptococcus	57	59.3
3. Hemolytic Streptococcus	7	7.2
4. Gram-negative Diplococcus	18	18.7
5. <i>B. thetoides</i>	11	11.4
6. Unidentified Gram-negative Bacilli	10	10.4
7. <i>Streptobacterium fetidus</i>	9	9.3
8. Unidentified Gram-positive Bacilli	7	7.2
9. <i>Staphylococcus</i>	6	6.2
10. <i>Clostridium Aetioletidus</i>	5	5.2
11. <i>B. pseudodiphtheriae</i>	4	4.1
12. <i>Clostridium sporogenes</i>	4	4.1
13. Gram-positive Diplococci	3	3.1
14. <i>Clostridium putrificus</i>	3	3.1
15. Gram-positive Streptobacillus	2	2.0
16. <i>B. bifidus</i>	2	2.0
17. Gram-positive Bacillus Producing Red Colonies	2	2.0
18. <i>Clostridium welchii</i>	1	1.0

(Courtesy, Annals of Surgery, April, 1938)

genicum was found in 89 cases. The author was unable to find previous descriptions of this bacterium being present in peritoneal exudate secondary to appendicitis. It was of interest to find anaerobic streptococci in 64 cases, and in almost every instance these grew in close symbiosis with the *B. melanogenicum*. The clostridium group was found in only 13.5 per cent of the cases. In 91 cases more than 1 anaerobic bacteria was cultured, 2 species of anaerobes in 42 cases and 3 in 45 cases. The average number of species of both aerobic and anaerobic in the entire series was 4.28. The same organisms were found in both the peritoneal exudate and the metastatic abscesses. A comparison showed very little difference between the type of species in the fatal and nonfatal groups. It was found impossible to predict the course of appendicitis peritonitis from

the type of bacteria isolated in any given case.

Carrying this study farther, Altemeier¹²⁷ investigated the cause of the putrid odor so frequently attributed to the *B. coli*. By inoculating sterile pus obtained from a tuberculous empyema, and from a pyarthrosis of a shoulder joint he found that the *B. coli* had no ability to form putrid pus. However, the characteristic putrid odor was caused by the presence and growth of anaerobic bacteria, chiefly the *B. melanogenicum* and anaerobic streptococci.

Vilaro¹²⁸ studied 25 cases of appendicitis in an attempt to show the relationship between the type of infective lesions in an organ and the phase of bacteria producing them. Aerobic cultures on plain agar were made from the material obtained by stroking the mucosal walls of the appendix. The bacteria isolated from selected colonies were studied in the usual methods and also for agglutination with tripaflavine and for pathogenicity by intraperitoneal inoculation of guinea pigs. In 20 cases (80 per cent), only *B. coli* developed, in 3 (12 per cent) bacteria which were not definitely identified, and in 2 (8 per cent) there was no growth. Only the *B. coli* colonies were studied, the smooth type predominated, the rough and medium forms were rare.

The histological findings in the appendices from which only smooth colonies developed consisted essentially of acute or subacute inflammation with hemorrhagic foci, leukocytic infiltration, and frequent abscess formation. In the appendices from which the rough and intermediate colonies also developed, the basic characteristic of the lesions was a focal or diffuse hyperplasia of the subserous intramuscular, or subserous connective tissue, which in some instances was so great as to disrupt or replace entirely the muscular coat.

In a study of the cultures taken from 55 patients suffering from gangrenous appendicitis associated with spreading peritonitis, Bower,¹²⁹ *et al.*, found 41 were positive for aerobes and 35 for anaerobes; a number of cultures showed both. Of the aerobes, *B. coli* was present in 27 (65.85 per cent); streptococcus in 16 (39.02 per cent), multiplicity of associations was found in 72 (97 per cent). *B. coli* alone was more frequent than any other—10.53 per cent. Of the anaerobes, *Cl. welchii* was present in 21 (60 per cent); alone in 12 (34.29 per cent); associated with other anaerobes in 7 (20 per cent), with anaerobes or aerobes in 14 (30 per cent). A multiplicity of associations was present in 76.18 per cent. They found that *Cl. welchii* apparently was present in the same ratio in spreading peritonitis in human beings as in induced spreading peritonitis in dogs.

To support their feeling that *Clostridium welchii* plays an important rôle in the spreading peritonitis of appendiceal origin, Bowers,¹³⁰ *et al.*, demonstrated that individuals recovering from attacks of appendicitis have sufficient antitoxin in their serum to protect pigeons against the toxin of *Clostridium welchii*. In 10 apparently normal adults used as controls, the incidence of antitoxin in the blood serum was zero, in 9 patients convalescing or recovered from acute unperforated appendicitis, the incidence of demonstrable antitoxin in the blood serum was 22.2 per cent, in 15 patients with active or quiescent pelvic peritonitis the incidence of demonstrable antitoxin was 46.6 per cent, and in 28 patients suffering with or recovered from spreading peritonitis secondary to perforative appendicitis, the incidence of demonstrable antitoxin in the blood serum was 69 per cent. It was found that the antitoxin

could not be recovered from the blood of patients before the seventh day of the disease.

Etiology—From Spencer's¹³¹ paper one concludes that acute appendicitis has a nationality, probably as a result of diet, as well as a predilection for the well-to-do class. It is twice as common in the United States as it is in Great Britain; natives of the West Indies, India, and China are rarely, if ever, affected unless they have adopted the European diet.

In an investigation of various factors which may have etiologic value, he found 75 per cent of the appendices affected were bent, 75 per cent contained fecaliths or liquid feces; 35 per cent of the patients had sore throat. He feels that the formation of fecaliths are linked with the reduction of the cellulose intake as suggested by Short. Once the fecalith is present in the appendix, it becomes regarded as a foreign body and inflammatory reaction is set up around it. The muscular response may be sufficient to force it into the cecum, if the fecalith is small; however, when it is too large, edema, impaired circulation, impaired lymphatic drainage and eventual gangrene may follow.

Wangensteen¹³² and his colleagues, realizing that the appendix secretes a fluid (1 to 2 cc daily), have renewed interest in the obstructive origin of appendicitis. It has been pointed out that in the severe forms of appendicitis in man, a demonstrable obstruction, frequently a fecalith, is usually found. Observations suggest that the secretory mechanism is less active in the aged, and that the cecal opening is much larger in the infants, therefore the relative infrequency of appendicitis. The hazard of a closed loop with the small intraluminal capacity of the vermiform appendix, associated with continual secretion seems a logical explanation for appendicitis.

Lymphoid hyperplasia and inflammatory swelling may account for those cases where fecalith and foreign bodies are not found.

The rôle of lymphoid hyperplasia in the production of mild acute, subacute, or recurrent appendicitis has been investigated by Gray and Heifetz.¹³³ The records of 14,000 appendectomies were examined and 51 were observed in which definite lymphoid hyperplasia could be made out. The clinical symptoms in these patients simulated those of mild acute appendicitis. The clinical picture is explained on the basis of an obstruction by hyperplasia of the lymphoid follicles in a narrow lumen organ.

In an attempt to explain the existing confusion as to the cause of appendicitis, Connell¹³⁴ explains the obstruction not due to foreign bodies, fecaliths, mucous plugs, edema, neoplasm, strictures, stasis, angulation, or deformity, on a neuromuscular basis. He points out that the ileocecal region has a dual parasympathetic innervation, which fact permits the possibility of over- or underinnervation. Although the existence of a true sphincter at the appendicocolic junction is denied, circular muscle is present. With the necessary factors present, the author feels that we are justified in accounting for some of the obstructions on this basis.

Rarely, foreign bodies are the etiologic factor in acute appendicitis. Rentschler¹³⁵ reports a case of acute perforative appendicitis in a girl of 17 years which was caused by a common straight pin. No history of swallowing the pin could be elicited. The clinical course in this case was smooth.

Appendicitis due to *trauma* is important from a medicolegal standpoint as well as from the high mortality rate which it seems to carry. Burgess¹³⁶ states that in a series of 50 cases Kelly had a 50 per cent mortality. Gangrene

and perforation are frequent findings in these cases. He reports the case of a 46-year-old male who for 2 weeks had been pressing the butt of a pneumatic drill against his lower right quadrant, when he suddenly experienced a severe pain in his abdomen which prostrated him. At operation 24 hours later, the tip of the appendix was found amputated. Convalescence was uneventful—compensation was allowed.

Fowler¹³⁷ concludes that appendicitis is a disease and not an accident; it cannot be produced by trauma alone. One must evaluate the effects of trauma upon (1) the normal appendix; (2) the pathologic appendix. The question of correct evaluation of trauma rests upon (1) whether the patient has had previous attacks, (2) character of the force; (3) the time element, (4) the bridging of symptoms from the accident to operation; (5) pathologic findings at operation; (6) the final microscopic diagnosis. To admit that genuine primary traumatic appendicitis exists, the following requirements must be met: (1) There must be no history of previous attacks. (2) The causative traumatism must be capable of reaching and affecting the appendix. The injuring body must be large, the force direct, blunt, violent, and of limited duration. (3) The effects of trauma must be immediately experienced, merge into those of acute appendicitis, must be properly reported, be disabling, require medical attention and operation at once. (4) True traumatic lesions of the appendix must be operatively demonstrated, namely, frank contusion, hematoma, or effusion in the wall of the mesentery, genuine rupture, laceration or puncture. (5) There must be a superimposed acute inflammation of the appendix, the result of the traumatic lesion diagnosed microscopically, and no evidence of chronic pathology.

To admit the contributory or aggravating influence of trauma, the following postulates are essential: (1) A definite history of previous attacks. (2) The history of trauma must here also show a definite sequence and relationship to, and be correlated with, the operative findings. (3) The onset of symptoms characteristic of an exacerbation must develop at once and force the patient to stop work. (4) The occurrence must be properly reported. (5) The operative findings should show, conclusively, either genuine traumatic pathology with an added acute appendicitis or unquestioned pathology antedating the injury, with superimposed acute appendicitis. (6) The histology should indicate acute appendicitis. There are no proofs that chronic appendicitis can be attributed to trauma, if operation is delayed and chronic histologic pathology found trauma should not be considered the cause. If the acute attack subsided and a second attack occurs later, trauma should not be held responsible for the exacerbation.

Two cases of appendicitis due to trauma were reported by McCarthy and Magrath,¹³⁸ who feel that the appendix, like any other hollow viscus, can be ruptured by force, subject to tears in the mesentery, or occlusion of blood supply as a result of external trauma.

Symptoms—Wood,¹³⁹ in an attempt to re-emphasize the importance of recognizing a difference between primary acute inflammations of the appendix and primary acute obstruction in the appendix as taught by Sir David Wilkie, wrote letters to various medical schools in Canada, United States, and Great Britain. He asked these questions: (1) Does your school of medicine teach Wilkie's differentiation in appendicular disease? (2) Is such teaching emphasized as being important and lifesaving? The replies were: Canada, 2 negatives; United

states, 2 positive and 1 negative replies, Great Britain, 3 positives.

He quotes from Wilkie's original article: "If we set out by recognizing 2 different types of acute disease of the appendix, namely, acute inflammation and acute obstruction, then not only does the understanding and teaching of symptomatology of acute appendicular disease become much more simplified but the early diagnosis of such disease becomes invariably more confident and more correct."

From the standpoint of symptomatology, acute inflammation of the appendix is the same as acute inflammations in any location, the patient is acutely ill, pain is not acute or cramp-like, the temperature, pulse, and leukocytes are elevated. In these cases immediate operation is not imperative. While in the obstructive type there is no fever, leukocytosis, or pulse elevation, the pain is acute or cramp-like accompanied by reflex irritation of the rest of the gastrointestinal tract, evidenced by nausea, vomiting and at times diarrhea. The diagnosis of obstructive type of appendicitis requires immediate operation because the peritoneal cavity does not have time to wall the process off after perforation. It must be understood that acute obstruction may be superimposed upon an acute inflammation. When this occurs the character of the pain changes, becoming more severe and cramp-like; with this change in character of the pain the attitude of the attendant should change to one of urgent speed in removing the appendix. Infected thrombosis of the veins draining the cecal region, i. e., appendiceal and superior mesenteric, throws an entirely different light into the picture. It would be well to segregate these cases independent of whether their origin be in the obstructive type or the inflammatory type of ap-

pendicitis. Multiple chills pre- or post-operatively are considered warning signs and the treatment is ligation of the infected vein above the thrombus.

In reviewing the results obtained during the past 4 years in the management of patients suffering from acute appendicitis complicated by spreading peritonitis, Bower¹⁴⁰ found that in every instance where death occurred the surgeon did not diagnose the condition preoperatively. The most frequent error was failure to recognize early perforative peritonitis. The second most frequent error was inability to diagnose the gangrenous appendix in the preperforative state. The "lucid interval" as used in connection with gangrenous appendicitis is the symptom-free period preceding perforation, and is dependent upon factors which influence intra-appendiceal pressure. The subsidence of pain, remission of temperature, the absence of tenderness and the increased tension or rigidity are due in part to a reduction of intra-appendiceal pressure. The symptoms and signs of an acutely inflamed appendix, prior to the development of gangrene, are associated with and partially dependent upon increased intra-appendiceal pressure.

The diagnosis of the preperforative stage—"the lucid interval"—is dependent upon the history, the physical findings, noting the physical findings of the physician who first examined the patient, and a careful differential count observing the ratio of mature and immature neutrophils. Important points frequently missing from the clinical records are (1) The exact time the pain began, (2) whether or not a laxative was administered, the time of administration, the character, kind and size of dose or doses, and when and how much opiate or sedative was given before admission. Colicky abdominal pain, general at first, center-

ing about the umbilicus, and later localizing in the right lower quadrant, is still the most reliable symptom of acute appendicitis. Tenderness is the most important physical finding, and this one finding in the right lower quadrant is sufficient at times to make the diagnosis of appendicitis.

Varieties of Appendicitis—Acute Appendicitis—Strauss and Tomarkin¹⁴¹ have reviewed 1325 consecutive operations for acutely inflamed appendices, all so diagnosed by pathologic sections. There were 748 males, 577 females; 711 were between the ages of 10 and 30 years. The total mortality of 4.3 per cent (57 cases) was attributed to the fact that 1020 were operated within 48 hours; of these, 738 were operated within 24 hours. Localized peritonitis was present in 870 cases. Perforation occurred in 187 cases with a mortality of 11.2 per cent. Fecaliths were present in 184 cases (14 per cent), and was evidenced in 18 (36 per cent) of the fatal cases. In other words, the mortality in the presence of fecaliths was 3 times as high as in their absence.

Realizing that a drain in the abdomen is usually considered walled off in 14 to 20 hours, they studied the effects of drainage on mortality, morbidity, and complications. Of the 187 cases of ruptured appendicitis with 21 deaths, 110 had intra-abdominal drainage, 77 had no drainage of the peritoneal cavity. There were 16 deaths in the group with drainage (14.5 per cent mortality) as contrasted with 5.3 per cent mortality in the undrained cases. The authors feel that these figures are important in emphasizing the dangers of drainage, which should be reserved for the localized walled-off abscesses. There were 31 cases operated in which drainage was the only procedure with 6 deaths or 19.3 per cent mortality. Complications were

more common in the drainage cases; pelvic abscess was 2 to 4 times as frequent and fecal fistula was 7 times as common.

Following the study of a series of 541 cases in 1932, Fairchild¹⁴² drew these deductions: (a) When the disease is seen before actual rupture and before general peritonitis has complicated the picture the mortality should be *nil*; (b) the relation of age to operative risk is a major consideration; the mortality per cent for all in the first 4 decades is to the mortality per cent for all in the last 4 decades as 1 is to 10; (c) the elapsed time between onset and operation is vital, the risk for all those coming to surgery in less than 24 hours being to the risk for all those coming after this period as 1 is to 8; (d) unruptured gangrenous appendices carry no more hazard than acute catarrhal provided they can be removed intact (surgical technic can and should be altered to make this possible); (e) in appendicitis complicated by general peritonitis, treatment of the appendix is secondary in importance to the treatment of the peritoneum. He then altered his technic as follows:

GROUP I	GROUP II
1 Often some delay in operating	1 No avoidable delay.
2 Patients in first and second half of life treated similarly	2 Surgery in second half of life reduced to simplest form
3 Practically all right rectus incision	3 Practically all gridiron incision
4 Drainage without appendectomy in 12 cases	4 Drainage without appendectomy in 38 cases
5 Gangrenous appendices freed by sense of touch	5 Gangrenous appendices removed through large incision under direct vision

A comparative study of 515 similar cases treated according to the above methods showed: That in 418 cases operated under the classification of acute appendicitis there were no deaths. In the original series of 396 cases there were 3 deaths. That in the ruptured group there were 3 deaths in 51 cases, as against 4 deaths in 66 cases in the original group; practically the same mortality percentage. Appendicitis complicated with peritonitis resulted in 4 deaths in 41 cases (9.8 per cent) as against 17 deaths in 79 cases (21.5 per cent) in the first series. The general mortality in the second series was 1.37 per cent as against 4.4 per cent for the first series.

Reporting on 1500 operations done for appendicitis, acute and chronic, Ray¹⁴³ classified them as: Acute unperforated, 727 cases, 2 deaths, mortality 0.27 per cent, appendicitis perforated and local abscess, 99 cases, 5 deaths, mortality 5 per cent, appendicitis perforated and spreading peritonitis, 60 cases, 12 deaths, mortality 20 per cent. General mortality of this group was 2.1 per cent. Operated on as acute appendicitis by mistake 127 cases, 2 deaths, mortality 1.5 per cent. Operated upon as chronic appendicitis 487 cases, 0 deaths—general mortality for this group 0.32 per cent and for the entire series 1.4 per cent. Conservative therapy was not used in these cases. Of these cases, 65 per cent were in the second and third decades, the youngest being 6 weeks (associated with strangulated hernia), the oldest being 83 years. Sex was showed a slight predomination of males, 52 to 48, greater under 12 years of age, 60 to 40. The obstructive phase considered important, also the lymphocytic element. In this series only 13 per cent of all acute cases had fecaliths, the incidence being greater in the severe forms, acute cases without perforation 11 per cent, compared to 28

per cent in the perforated cases. Seeds, splinters of wood, hair bristles, and other foreign bodies were found in less than 1 per cent. Intestinal worms in 7 acute and 7 nonacute, 12 oxyuris vermicularis, 1 ascaris lumbricoides, 1 tenia saginata. In 3 cases trauma appeared to play some part. Seasonal variation and epidemics as well as the frequent association with upper respiratory infection appeared to have some significance. Tuberculosis associated with acute infection was found in 4 cases. Carcinoid tumor in 3 cases. In 64 per cent of the acute cases there was no previous attack and the figures indicated that the appendix is more likely to perforate during the first attack than at subsequent attacks. Cathartics had been taken in 26 per cent of all the cases, in 19 per cent of the acute unperforated cases, and 43.5 per cent of the cases with perforation or abscess.

Flannery¹⁴⁴ studied the records of 440 with a final diagnosis of appendicitis. Twenty-three were not operated upon. Twenty girls and women were submitted to gynecologic operations and the appendix was incidentally removed, and in 1 adolescent male the appendix was not found. This leaves 396 cases of appendicitis in which operation was performed, 69.4 per cent were between 11 and 30 years, 60.2 per cent were females, 39.8 per cent males. The average time from onset of attack to hospitalization was 34.8 hours. Previous attacks were recorded in 55 per cent. In 29.1 per cent of the 189 cases of acute appendicitis the appendix was gangrenous on admission and in 63 per cent of these it had perforated. Cathartics were taken by 69, and 4 were given enemata before admission. Of the 9 deaths, 6 had taken some cathartic by mouth. Of 33 ruptured appendices, 15 had cathartics and 1 an enema. The mortality was a small

TABLE IV
ANALYSIS OF DEATHS

Year	No	R S	Age	Days Ill	Catharsis	Incision	Operative Findings	Complicating Factors	Cause of Death	Days P O
1927	1	W M	24	3	0	R R	R G app Abs pent		Gen peritonitis	14
1927	2	C F	10	2	0	R R	R G app Abs pent	Rheumatic fever	Gen peritonitis	6
1927	3	W F	50	1	0	McB	Chr app	Pneumonia, urine retention	Pneumonia	12
1928	4	W F	60	1	0	R R	S app	Myocarditis	Cerebral embolism	1
1928	5	W F	41	1	0	R R	R G app Abs		Gen peritonitis	9
1928	6	W M	40	7	0	R R	G app	Septicemia Pneumonia	Septicemia Pneumonia	24
1928	7	W F	40	2	0	McB	R G app Pent		Gen peritonitis	5
1928	8	W F	3	3	1	R R	R G app Pent		Gen peritonitis	3
1928	9	W M	16	6	1	R R	R G app		Gen peritonitis	1
1928	10	W M	48	7	1	McB	R G app Abs		Gen peritonitis	7
1929	11	W M	5	2	0	R R	R G app Pent		Gen peritonitis	2
1930	12	W F	16	5	0	M	R G app Pent		Gen peritonitis	11
1930	13	W F	3	2	0	McB	R G app Abs		Gen peritonitis	1
1930	14	W M	56	1	0	McB	R G app Perit Thrombosis of mesoappendix		Pylephlebitis Pneumonia	29
1930	15	W M	5	1	0	McB	R G app	Pneumonia	Gen peritonitis	8
1931	16	W M	39	7	0	McB & R R	R G app Pent		Gen peritonitis	5
1931	17	W F	56	1	0	R R	S app		Gen peritonitis	6
1931	18	W M	46	7	0	McB	Chr app	Pneumonia	Pneumonia	5
1931	19	W F	15	1	0	McB	G app Perit		Gen peritonitis	5
1931	20	W M	16	1	0	McB	R G app Pent		Subphr Gen peritonitis	25
1931	21	C M	21	1	0	R R	G app Perit		Gen peritonitis	2
1931	22	W M	31	1	1	McB & R R	R G app Pent		Gen peritonitis	4
1932	23	C M	21	14	1	McB	R G app Pent		Gen peritonitis	10
1932	24	W M	12	2	0	R F	R G app Pent		Subphr Empyema	17
1932	25	W M	43	2	0	R R	R G app Abs	Pneumonia and empyema	Pneumonia, empyema	38
1933	26	W F	7	2	0	McB	R G app Perit		Gen peritonitis	1
1933	27	W M	4	8	0	R R	R G app Perit		Gen peritonitis	1
1933	28	W F	54	4	0	McB	G app	Obesity-Diabetes mellitus	Diabetic Coma Gen peritonitis	2
1933	29	C F	55	3	0	McB	R G app Abs Perit		Gen peritonitis	1
1933	30	W F	59	1	0	R R	R G app Pent		Gen peritonitis	3
1934	31	W F	28	1	0	McB	R G app Perit		Gen peritonitis	1
1934	32	W F	73	3	0	R R	R G app Pent		Gen peritonitis	5
1934	33	W M	17	4	0	R R	R G app Abs		Gen peritonitis	2
1934	34	W M	14	14	0	R R	R G app Abs	Fecal fistula subphr	Subphr Gen peritonitis	15
1935	35	C M	32	3	0	R R	R G app Perit Pylephlebitis		Pylephlebitis - I Abs	3
1935	36	W M	30	4	0	McB & R R	R G app Perit Pylephlebitis		Pylephlebitis - L Abs, subphr	42
1936	37	C F	52	1	0	McB	R G app Perit	Diabetes	Diabetes Gen peritonitis	13
1936	38	W M	19	3	0	McB	S app		Gen peritonitis	5
1936	39	W M	30	2	0	McB & R R	R G Perit		Gen peritonitis	6
1936	40	W F	40	2	0	R R	R G app Perit Pylephlebitis		Gen peritonitis	8

* Appendix not removed

† Not drained

‡ Enterostomy

§ Ileocolic veins ligated

M - Male

F - Female

W - White

C - Colored

R - Ruptured

G - Gangrenous

S - Suppurative

McB - McBurney

R R - Right rectus

M - Midline

App - Appendix

Abs - Abscess

Subphr - Subphrenic abscess

I - Liver

(Courtesy Surg, Gynec and Obst, (Feb) 1938.)

TABLE V
IMPORTANT SIGNS AND SYMPTOMS PRESENTED IN THIS AND OTHER SERIES OF
CASES OF APPENDICITIS

Signs and Symptoms	Kline, 1935	Reid and Others, 1936	Boyce and Others, 1936	Finney, 1933	Collins, 1938
Nausea	51.0%	78.0%			56.66%
No Nausea			2.14%		
Vomiting	45.0%	73.0%			53.33%
No Vomiting			2.14%		
Constipation	31.0%		1.71%		28.46%
Diarrhea					13.43%
Pain in Right Shoulder					11.72%
Fever	50.0%				68.89%
High Fever (102-105° F)			4.8%		11.17%
Normal Temperature	32.0%		20.8%		18.75%
Subnormal Temperature	16.0%				12.36%
Leukocytosis (over 10,000 cells)	46.0%				69.43%
White Blood Count Below 10,000			17.2%		30.56%
Average Leukocyte Count		17,200		17,669	11,870
Average Polymorphonuclear Count				85.5%	83.0%
Polymorphonuclear Count Over 80 per cent	41.0%				58.17%
Erythrocytes in Urine	9.0%				13.85%
Albuminuria	28.0%				23.71%
Casts in Urine	12.0%				10.11%
Pyuria in Catheterized Urine Specimen					20.24%
Localized Pain in Right Lower Quadrant of Abdomen	81.0%				18.88%
Pain Elicited in Right Flank					63.31%
Muscular Spasm Localized in Right Lower Quadrant of Abdomen	52.0%				47.20%
Limited Excursion of Right Side of Diaphragm					7.59%
Board-like Muscular Rigidity	10.0%				4.52%
Sedimentation Rate Abnormal					8.11%
Use of Penrose Drains	42.0%				34.84%
Rebound Abdominal Tenderness	35.0%				67.64%
Abdominal Pain		94.0%	96.3%		83.12%
Rectal Tenderness		44.0%			50.07%
Typical History of Appendicitis		53.0%			18.91%
Average Temperature		100.1 F			100.4 F
Average Pulse Rate		99			88
Typical History of Pelvic Disease			0.59%		6.62%
Typical History of Perforated Peptic Ulcer					18.11%
Typical History of Cholecystitis			0.44%		7.06%
Typical History of Renal Disease			0.07%		11.17%
Typical History of Ectopic Pregnancy			0.07%		0.00%
Association with Respiratory Disease			7.55%		13.85%
Association with Alcoholism			1.43%		9.57%
Association with Dietary Indiscretions			3.03%		16.49%
Pain in Left Side of Abdomen Only			0.75%		1.19%
No Localization of Pain in Right Lower Quadrant of Abdomen			2.25%		18.24%
Advanced Dental Caries, Pyorrhea					55.79%

(Courtesy, Arch Surg, May, 1938)

fraction over 2 of every 100, while for the acute gangrenous perforated cases it was over 2 of every 10. In half the cases death was due to peritonitis. The right rectus incision was used in 234 cases and the McBurney in 140 cases. In-

version of the stump was done in all cases except the abscess or peritonitis.

Sprague,¹⁴⁵ *et al.*, studied 1463 cases of appendicitis with 40 deaths or a general mortality of 2.73 per cent. The cases were classified: Ruptured 122

TABLE VI

INCIDENCE OF POSTOPERATIVE COMPLICATIONS IN REFERENCE TO TYPE OF INCISION USED

	Type of Incision			Totals
	Muscle-Splitting	Midright Rectus	Midline	
Number of cases	277	313	161	751
Postoperative complications				
Postoperative morbidity . .	77 (10.25%)	178 (23.70%)	141 (18.75%)	396 (52.73%)
Pelvic abscesses	24 (3.20%)	31 (4.13%)	42 (5.59%)	97 (12.92%)
Secondary closures of wound	0 (0.00%)	10 (1.33%)	21 (2.80%)	31 (4.13%)
Hernias after incision	0 (0.00%)	17 (2.26%)	34 (4.53%)	51 (6.79%)
Average number of days in the hospital	16	23	27	
Average time spent at performing operation	37 min.	51 min	62 min	
Sex—Males	251 (33.42%)	172 (22.90%)	48 (6.39%)	471 (62.72%)
Females	26 (3.46%)	99 (13.18%)	155 (20.64%)	280 (37.28%)
All deaths	12 (1.60%)	18 (2.40%)	28 (3.73%)	58 (7.72%)

(Collins Arch Surg, May, 1938)

cases, 31 deaths, mortality 25.4 per cent; gangrenous 129 cases, 4 deaths, mortality 3.1 per cent, suppurative 169 cases, 3 deaths, mortality 1.8 per cent; acute, subacute, chronic 1043 cases, 2 deaths, mortality 0.19 per cent. A definite plan of technic was followed; acute cases with dehydration were given glucose and saline preoperatively, the McBurney incision was used in all cases when the diagnosis was reasonably certain; the appendix was removed in all but 3 cases; the stump was crushed, ligated and inverted, a chill suggested thrombophlebitis and the mesoappendix was ligated high, for multiple chills a high ligation of the ileocolic vein was done; the appendix was immediately removed in all acute cases; localized abscess was treated by extraperitoneal drainage if possible, otherwise packed with iodoform and later drained. Anesthesia was open drop ether for colored patients and children, a few spinal, mostly nitrous oxide oxygen ether. See Table IV for analysis of the fatal cases.

Bliss and Heaton¹⁴⁶ reported 2100 operations done for appendicitis performed at the Station Hospital, Fort

Sam Houston, Texas, with only 10 deaths, a mortality of 0.47. Of these, 286 (13.62 per cent) were of the chronic or interval type. Analyzing them according to age we find that a relatively small number were in the dangerous periods of life, *i e*, 36 (1.69 per cent) were 10 years or under and 23 (1.11 per cent) were 50 years or over. Further analysis shows that only 54 (2.58 per cent) were ruptured with peritonitis, and 7 of the 10 deaths were in this group, a mortality of 12.9 per cent. The type of incision seemed to play no important part; the McBurney was used in 397 with 4 deaths, the transverse in 1129 with 3 deaths, the right rectus in 464 with 3 deaths. It is the author's opinion that this low mortality rate is due to early admission to the hospital with prompt operation. They feel that spinal anesthesia, which was used in 1930 cases, contributes to the lower mortality rate.

Retrocecal and Retrocolic—In a series of 3003 consecutive appendectomies performed for acute appendicitis, Collins¹⁴⁷ encountered 751 cases (25 per cent) of acute retrocecal appendi-

citis; 471 (62.72 per cent) were males. The average age was 29.7 years; a noticeable increase in the incidence of this type of appendicitis was found in the later decades. Race and season showed nothing important. In 267 cases (35.55 per cent) a history of appendectomy in members of the family was obtained.

The past histories revealed that 301 (40 per cent) had frequent previous upper respiratory infections, in 111 of these

patients had had previous operations of various types without alleviation of symptoms; 64 (8.52 per cent) had cholecystectomies; 52 (6.79 per cent) various gastric operations for ulcer; 2 (0.27 per cent) nephropexies; 45 (5.99 per cent) various gynecologic procedures, and 31 (4.13 per cent) major pelvic operations.

Nausea, headache, flatulence, heartburn, regurgitation, insomnia, constipation and lack of appetite disappeared in

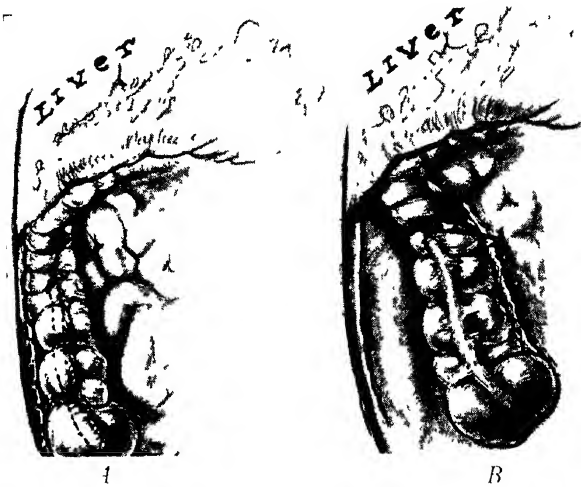


Fig. 1. A—Retrocolic appendix. B—Ascending colon reflected mesially so as to expose appendix. (Courtesy, *Annals of Surgery*, May, 1938.)

such an infection preceded their present acute abdominal complaints by 8.4 days. 136 (18.1 per cent) had chronic recurrent sinusitis, 317 (42.21 per cent) still have their tonsils, of these 293 (38.88 per cent) had chronic tonsillitis. Four hundred and sixty-six persons (62.05 per cent) had previous similar abdominal attacks, 151 (20.11 per cent) had been told by a physician to have operations. The various other abdominal diagnoses made prior to the acute attacks were: Cholecystitis, 138 (18.39 per cent); gastric or duodenal disease, 99 (13.8 per cent); disease of right kidney or ureter, 71 (9.45 per cent); pelvic inflammation, 44 (5.86 per cent). Many of the

73.4 per cent of cases after appendectomies. Distress from cheese, rich and greasy foods, and raw fruits frequently vanished after appendectomy. Arthritic symptoms were improved in some of the older patients. The symptoms suggestive of chronic gall bladder or ulcer were frequently relieved. For more accurate summary of history consult Table V.

It is interesting to note that the best results were obtained when the muscle-splitting incision was used from the standpoint of mortality as well as morbidity. The details are best seen in Table VI. It will be noted that the hospital days, operative time, wound complications, and hernia are diminished. In

TABLE VII
RÉSUMÉ OF DATA RELEVANT TO 6 CASES OF RETROCOLIC APPENDICITIS

Name and Date	Age and Sex	Onset Before Oper	Laboratory Data	Condition at Oper.	Complications	Days in Hospital	Cathartic	Result
1 D C 7-28-25	29 M	18 hrs	W B. C. 7600 Polys 70% Urine negative	Retrocolic Not ruptured Drained	Ruptured during removal Phlebitis	59	No	Good
2 W. P 11-3-35	27 M	26 hrs	W B. C. 13,800 Polys 80% Urine negative	Retrocolic Not ruptured Drained	Ruptured during removal Hemorrhage Fistula	36	No	Good
3 J R 1-4-37	47 M	12 days	W B. C. 22,650 Polys. 90% Urine negative	Retrocolic Abscess Drained	None	25	Yes Diar- rhea	Good
4 N R 2-15-37	28 F	24 hrs	W B C 21,000 Polys 93% Urine negative	Retrocolic Acute	None	10	Yes	Good
5 J E 6-12-37	26 M	24 hrs	W B C 15,200 Polys 85% Urine negative	Retrocolic Acute	None	11	No	Good
6 K Y 1-6-37	21 M	48 hrs	W B C 20,800 Polys 85% Urine negative	Retrocolic Acute	T 105.4° F Postoper	21 approx	Yes Diar- rhea	Good

Résumé of Table—Six males and 1 female Onset before operation One to 12 days Complications Two appendices ruptured during removal, 1 phlebitis; 1 hemorrhage and fecal fistula Days in hospital Longest, 59, shortest, 10 Average for Cases 1 and 2, 47.5 days, Cases 3 and 6, 16.7 days

(Courtesy, *Annals of Surgery*, May, 1938.)

only 12 of the 58 deaths was the muscle-splitting incision used

Localized abscesses were drained by simple Penrose drains, which were removed on the twelfth postoperative day Drainage was not instituted for general peritonitis, the peritoneum being closed tightly, but the rest of incision loosely closed In 97 cases pelvic abscess requiring operative drainage occurred (mid or right rectus incision had been used in these) In the entire series there were 58 (77.2 per cent) deaths

Marbury¹¹⁸ feels that it is correct to speak of the appendix as retrocecal when it is limited by the space behind the caput cecum, and retrocolic when it extends upward behind the ascending colon. Most retrocolic appendices are also retro-

peritoneal, but this does not follow in regards to the retrocecal type, which usually lies free and has a complete peritoneal investment He presents 6 cases of true retrocolic (and retroperitoneal) appendicitis, by which he means that the appendix is behind the ascending colon and cannot be seen or felt except at its base with the abdomen open (Fig 1) It occurs in about 7 per cent of the cases

The significant factors to consider are failure to have pain localizing over McBurney point, after the initial epigastric pain, nausea and vomiting, absence of muscle spasm of the anterior abdominal wall, a tender point in the loin or over the crest of ilium It is more characteristic of this type of appendix that, after

the initial onset, the patient does not complain of much pain, but since the infectious process remains and is continuous, pulse, fever, leukocytosis are important. Hematuria was not noted in these cases. Flexion of the thigh due to psoas irritation was a symptom. Early in the course these patients may become lethargic, and in the absence of definite localizing signs the condition may be considered medical rather than a surgical problem. Generalized peritonitis is not common in these cases, but grave consequences may result from a retroperitoneal spread. Subdiaphragmatic abscess, empyema, bronchial fistula, and psoas abscess are the most common complications due to this type of spread. The important data on these cases is summarized in Table VII.

The author feels that the McBurney incision is the one of choice in cases of appendicitis but when this condition is encountered it should be extended upward and downward even at the expense of severing the deep muscles. For retrocecal appendicitis the ascending colon is best mobilized, by division of the lateral leaflet, and reflected medially in order to expose the appendix for its entire length. In 2 cases in which this was not done the appendix was ruptured during removal, and in 1 of these a marked hemorrhage occurred which finally necessitated reflexion of the colon to control it.

McCorkle and Stevenson¹⁴⁹ report an interesting case of psoas abscess, rupturing in the upper right thigh of a 67-year-old man, from whom a ruptured retrocecal appendix, partially embedded in the psoas muscle, was removed 2 months after the abscess had closed. They state that: In 1642 Saracenus mentions a case of right groin abscess with spontaneous rupture, discharge of fecal material and lumbricoid worms followed

by spontaneous recovery; in 1813 Copeland reported a fecal abscess of the right groin from which an oval calculus was extracted and spontaneous closure followed; in 1865 Buck opened a perityphlitic abscess pointing in the right groin below Poupart's ligament from which a pin was discharged. The most striking case was one reported by G. W. Crile in which the abscess finally localized in the right popliteal space.

Chronic Appendicitis — Muller¹⁵⁰ has re-emphasized the fact that the term "chronic appendicitis" is a misnomer because true chronic inflammation is seldom found. However, true pathological conditions develop in the right iliac fossa which do produce symptoms commonly called chronic appendicitis. "Obstruction of the lumen of the appendix by stricture, kinks, or concretions will act in a manner similar to obstruction in other parts of the intestinal canal, namely, by allowing increased peristalsis, distention of the lumen, and consequently pain." Adhesions about the appendix, due to previous acute attacks, peritoneal bands (membranes), and a miscellaneous group which includes worms, axillary neuromas, tumors, all produce the symptom complex. The misplaced appendix (retrocecal, retrocolic) frequently cause symptoms.

The *diagnosis* should be made by careful history and physical examination which includes a consideration of body habits. While a complete gastroenterologic examination, including roentgenograms, gastric analyses, stool examination, blood counts, Wassermann tests, are of value in obscure cases the expense is prohibitive and the results unnecessary in the average case. Ptosis, chronic gallbladder disease, tubo-ovarian disease, mesenteric adenitis, sacroiliac disease, osteoarthritis of spine, intercostal neuralgia, stricture of ureter, ureteral cal-

TABLE VIII
FREQUENCY OF SYMPTOMS IN CHIEF COMPLAINT

Symptoms	Number of Patients	Percentage
Constipation Including Alternation With Diarrhea	28	82
Constipation Alone	24	71
Generalized Abdominal Distress or Pain	23	68
Presence of "Gas" and Belching	17	50
Nausea With or Without Vomiting	15	44
Pains in Lower Right Quadrant	11	33
Nervousness	8	24
Constipation Alternating With Diarrhea	8	24
Fatigue, Lassitude, or Exhaustion	7	21
Diarrhea Alone	3	12
Laxative Habit	27	78

(Courtesy, Pennsylvania M. J., August, 1938)

culus, periureteral adhesions, are to be considered in evaluation of the cases.

In 1 series of 105 cases who had only an appendectomy for chronic appendiceal symptoms, 103 were followed and 89 (86 per cent) were completely relieved. In a similar series of 184 cases at another hospital, Muller received replies from 100, of which 93 were symptom-free and 7 were unimproved. The unimproved patients were those who had epigastric symptoms.

In an attempt to determine whether or not there is a clinical entity of chronic appendicitis, Shelly¹⁵¹ studied a series of 881 cases in which appendectomy had been performed. Of these cases, 704 (80 per cent) were followed for an average of 12½ months; 87 per cent had no return of symptoms.

The percentage of follow-up cures was low when no inflammatory changes were present, cases involving atrophic appendices giving the lowest figure. Inflammatory changes in the appendix or normal appendix with associated adhesions or fecaliths both gave high percentage of follow-up cure. From a clinical standpoint the following points are important: (a) In the presence of a history of nausea and vomiting or constipation, especially in women, particular care must be exer-

cised in selecting the case (b) The more definite and localized the physical finding, the better the chance of cure (c) The expectation of cure is excellent when the history is of more than 1 attack within a period of 1 year or less, much poorer when attacks are less frequent and poorest when the operation is done for the first attack. In this series there were 4 deaths which were due to (1) pulmonary edema (death 30 minutes after operation), (2) peritonitis (seventh postoperative day, culture streptococcus hemolyticus), (3) pulmonary embolus (eleventh day postoperatively), (4) purpura hemorrhagica, acute pericarditis, chronic fibrinous pleurisy (2 months after operation). When a patient has been operated upon because of symptoms of acute or subacute appendicitis, and instead 1 of the types of chronic appendicitis (adhesions or fecaliths without inflammation) is found, the expectation of a permanent cure is excellent.

Atypical forms of chronic appendicitis show symptoms of gastric diseases, colitis, or cholecystitis, without any pain, spontaneous or induced by palpation in the right lower quadrant, according to del Valle and Giordano¹⁵². For diagnosis, they suggest gentle massage of the iliac fossa with the abdominal muscles

TABLE IX
MOST VALUABLE DIFFERENTIAL DIAGNOSTIC SIGNS OR SYMPTOMS

Signs or Symptoms	Number of Patients	Percentage
Cases Noting Precipitation or Aggravation of Symptoms by Stress and Strain	30	88
Cases Noting Spastic (or Diarrheal) Types of Stools (small balls, pencil-form, ribbon-shape, etc.)	26	87
Presence of Unstable Nervous Systems (marked nervousness, crying spells, neurasthenia, neuroses, etc.)	29	85
Presence of Poor Living and Hygienic Habits (food-bolting, meal-skipping, inadequate sleep, no time for defecation, heavy smoking, alcoholism, etc.)	27	80
Presence of Definite Psychic or Emotional Strain (domestic difficulties, financial or business worries, overwork, etc.)	27	80
Patients Noting Gross Mucus in Stools	24	71

(Courtesy, Pennsylvania M J, August, 1938)

relaxed for a few minutes on 1 to 5 consecutive days. Pain, temperature elevation, or leukocytosis during this time indicates a chronic appendicitis. Massage is not advised in the presence of pain or tenderness.

Bigelow¹⁵³ sent a questionnaire to 167 persons on whom an appendectomy had been performed elsewhere, previous to operation at his clinic to cure chronic pain in the right side of the abdomen, diagnosed chronic appendicitis. None of these patients were relieved by the appendectomy. After his usual method of completely removing all so-called congenital bands, and membranes from the cecum, ascending colon or hepatic flexure, 136 (92 per cent) of 147 cases were completely relieved of their pain.

In a series of 34 selected cases who had been unrelieved of their symptoms by a previous appendectomy, Swalm and Morrison¹⁵⁴ found that 27 (95 per cent) were symptom-free within 1 year after treatment for spastic, irritable, or unstable colon. The frequency of symptoms in the chief complaint, and the most valuable differential diagnostic signs and symptoms are shown in Tables IX and X. A careful investigation of the patients' history and physical findings with

especial attention to emotional and psychic disturbances, domestic, social, and working environment, hygienic habits, size, shape, and mucous stool will be of value in differentiating spastic colon from chronic appendicitis, and thus avoid needless surgery.

W. W. Babcock,¹⁵⁵ in discussing this paper, states "But because many psychoneurotics have been treated by needless operation, we should not be blind to the fact that colonic spasm may be due also to a very definite reflex or toxic cause that can be eliminated by operation." His most marked case was that of a noted physician who despite various consultants suffered for 7 years until an obscure renal calculus was removed. He emphasized the teaching of the late Charles P. Noble, that when the irritability of the colon is expressed by a chronic diarrhea for which no other cause can be found, recovery will usually follow an appendectomy. The importance of this teaching was well illustrated by 2 cases observed while I was Dr. Babcock's assistant. A Jewish druggist, with all the emotional, psychic, social and economic background, came to his office complaining of vague abdominal pain and mucous diarrhea of several years'

duration. Much to my surprise his appendix was removed and to my greater surprise his symptoms were completely cured for 1 year after the operation despite continuation of the psychic factors. The other case was that of a medical student who during ward class told me of his attacks of diarrhea, lower right quadrant pain for which he was treated as a case of spastic colon; operation revealed a stricture, clubbing with pus in the distal lumen of the appendix; the spastic colitis has remained cured for the past 6 months.

Diagnosis—That abdominal pain and tenderness are the cardinal symptoms of appendicitis is realized by all. However, a lack of attention to the details as to type, character, duration and location of the pain is frequently the cause of errors in diagnosis. In a discussion of various causes for abdominal pain, Griffith¹⁵⁶ emphasized the extra-abdominal causes of pain such as coronary disease; lung, kidney and spinal cord lesions, osteomyelitis and tuberculosis of the spine. In 7 brief clinical abstracts he presented the aspects of abdominal pain occurring in lobar pneumonia, hydronephrosis, metastatic osteomyelitis of the spine, diabetic acidosis, coronary disease, and ruptured appendicitis. He emphasizes the importance of evaluating increase, decrease or constancy in the severity of the tenderness as a fairly good clinical guide. In discussing this paper, Simon-ton reveals that tenderness over the mastoid is often present in pneumonia due to phrenic nerve irritation, and may be a helpful diagnostic sign.

In reporting a rare case of acute appendicitis complicating pregnancy occurring in a female of 26 years who had a complete transposition of the viscera, Block and Michael¹⁵⁷ found that the pain was referred to the right lower quadrant of the abdomen. They state

that Poe, in a study of 46 reported cases of appendicitis (*insitus inversus viscerum*) found the pain to be right sided in over one-half of the cases. Other cases associated with right-sided pain have been reported by Courtney, Scopinaro, and DePoe. The authors are in accord with Kuntz who believes that in cases of appendicitis in transposition of the viscera referred phenomena ought to be localized on the right side, for even though the viscera are transposed their nerve supply remains the same.

Lintgen and Fry¹⁵⁸ studied 30 patients with acute pelvic inflammatory disease and 100 patients with acute appendicitis to determine the diagnostic value of the sedimentation test. In 90 per cent of the 30 cases of pelvic inflammation, the sedimentation of the erythrocytes was more rapid (between 11 and 40 mm) than normal. In 52 per cent of the patients with acute appendicitis, the rate was abnormal but not as rapid as in the pelvic inflammatory group. They conclude that the test can be depended upon to differentiate between these 2 conditions.

Contraction of the abductors as a new sign in appendicitis has been reported by Richet and Netter¹⁵⁹. The patient is placed on the back with mouth open, thighs half flexed, heels flat on the bed and knees touching, the muscular relaxation must be complete. Placing a finger on the internal edge of each knee, one exerts a pressure directed from within outward, tending to separate the knees one from the other and press them down with their external surface on the bed. Mild pressure constant and evenly applied on both sides must be used. It does not produce pain. The sign was found in 40 per cent of the cases of acute appendicitis, of equal frequency in children and adults. It was never found in other disorders of the

right side of the abdomen, although systematic search was made.

After a review of the literature and clinical observations in their own practice, Bustos and Lebron¹⁶⁰ state that

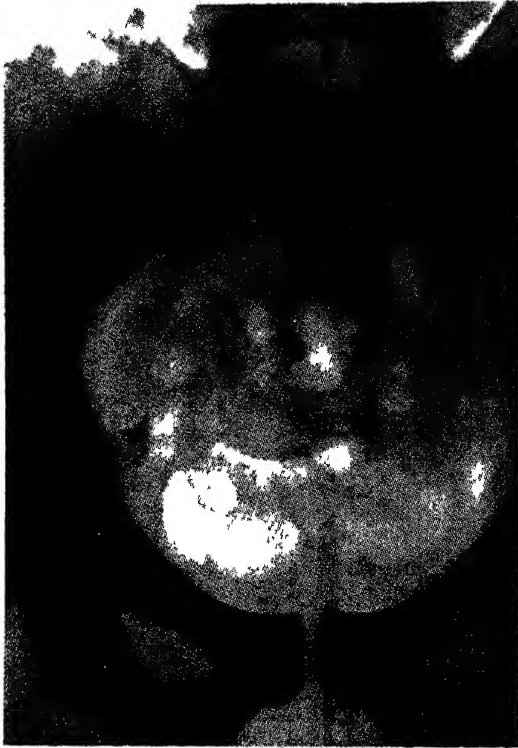


Fig 2—Roentgenogram made in December, 1936. The calcified fecalith can be seen lying in the right lower quadrant. At the time this film was made, there was nothing in the history or physical examination to point to trouble in the appendix. (Shelley Surgery, May, 1938.)

the Roysing sign is of no diagnostic value in appendicitis. They report in detail 2 cases of intestinal disease, presenting the sign although the appendix had been removed.

While acute appendicitis is generally regarded as being outside the field of radiology, Overend¹⁶¹ stresses the importance of plain roentgenograms in preventing diagnostic errors. The most valuable aid from radiology, however, comes in the proper study and evaluation of the chronic or recurrent cases. The author feels that this phase of gas-

trointestinal radiology has failed to keep pace with technical developments.

The roentgenological aspects of appendix examination are discussed relative to direct signs produced by intrinsic changes in the appendix and secondary changes of a morphological or functional nature referred to as indirect signs. Of the direct signs, luminal changes in the form of irregular narrowing, dilatation, or imperfect filling are the most important. Segmentation is of trivial importance as it may be due to active contraction. Filling defects due to corporoliths are also negligible. Stasis may be due to an organic cause, but it



Fig 3—The appendix as it appeared after removal. The fecalith shows as it presented at the time of operation. The slit in the wall toward the mesoappendix was made in removing the fecalith from the appendix for examination. (Shelley Surgery, May, 1938.)

also occurs in normal cases. Nonvisualization may or may not have diagnostic value. Many indirect signs have been described as being due to chronic appendicitis, but most of them must be

correlated with clinical findings. Localized tenderness over a visualized appendix is usually considered of definite value, but in the absence of such a shadow tenderness around the cecum may be significant. Demonstrable fixation, kinking or malposition may all be due to adhesions from a previous attack and are important in the diagnosis.

The importance of proper interpretation of roentgenographic findings are emphasized by a case reported by Shelley.¹⁶² The patient had definite roentgenologic evidence of a calcified fecalith in the appendix (Fig. 2) 4 months before an operation for acute perforated appendicitis was done. Had this finding been properly interpreted the patient would have been saved the suffering which nearly cost him his life. Appearance of appendix (Fig. 3) should be correlated with the roentgenogram.

Differential Diagnosis—Conditions producing abdominal pain which may simulate appendicitis have been arranged into 7 well-defined groups by Heyd.¹⁶³ He has further tabulated the conditions under each group as follows:

- I Conditions of the Gut-Tube
 - 1 Gastroduodenal ulceration
 - 2 Cholecystitis and pancreatitis
 - 3 Neoplasm of the colon, particularly of the cecum, and ascending colon.
 - 4 Acute mesenteric adenitis
 - 5 Meckel's diverticulitis
 - 6 Intestinal obstruction
 - 7 Hyperplastic tuberculosis of the cecum
 - 8 Regional ileitis
 - 9 Ulcerative colitis
 - 10 Spastic colitis
 - 11 Chronic constipation
 - 12 Intussusception
 - 13 Diverticulitis.
 - 14 Mesenteric vascular occlusion
- II Conditions Having Etiologic Origin from the Gut-Tube, but with the Major Pathologic Condition in Other Areas or Organs
 1. Subphrenic abscess
 2. Septic pylephlebitis.
 - 3 Retroperitoneal phlegmon.
 4. Perinephritic abscess.
 - 5 Hepatic abscess.
 - 6 Amebiasis.
- III. Conditions Arising from the Retroperitoneal Tissues.
 1. Acute hematogenous infection of the kidney.
 2. Nephrolethiasis
 3. Renal neoplasm
 4. Nephroptosis (Dietl's crisis).
 5. Ureteral calculus or stricture
 6. Perinephritic abscess.
 7. Retroperitoneal neoplasm, such as lymphosarcoma
 - 8 Right-sided pyelitis in children and women.
- IV Conditions, Primarily Thoracic, with Symptoms of Referred Pain
 1. Pneumonia.
 - 2 Pleurisy.
 3. Chronic tuberculosis of the lung
 4. Cardiac Disease.
 - 5 Intercostal neuralgia
- V Conditions Arising from Disease of the Peritoneum and Pelvis.
 1. Tuberculous peritonitis.
 - 2 Tubal disease.
 - 3 Ovarian cysts
 - 4 Ectopic gestation
 - 5 Pneumococcus peritonitis
 - 6 Torsion of omentum
 - 7 Gangrene of appendices epiploicæ.
 - 8 Pelvic allergy.
- VI Conditions Arising from Cerebrospinal Disease.
 1. Tabes dorsalis
 2. Spinal tumor
 - 3 Incipient meningitis
 - 4 Brain tumor
- VII. General Systemic Conditions or Remote Disease
 1. Sepsis, infarcts of the spleen, etc
 - 2 Lead poisoning
 - 3 Incipient diabetic coma
 - 4 Uremia
 5. Visceral manifestations, such as erythema exudative and angioneurotic edema
 - 6 Acute follicular tonsillitis.
 - 7 Herpes zoster.
 8. Peritonismus.

He further states that conditions most frequently mistaken for acute appendici-

tis are insidious perforation of gastric or duodenal ulcers, particularly the latter; atypical attacks of biliary colic, central pneumonia, diaphragmatic pleurisy, perinephritic abscess, ectopic gestation, and hemorrhagic cysts of the ovary, and ureteral calculus of the right side.

The transformation of cyclic pain to continuous fixed pain is suggestive of slow-ulcer perforation and due to drainage down the right paracolic fossa. The maximum pain and tenderness may be in the right iliac fossa. With a central pneumonia, the disturbance of the pulse rate and respiration rate in proportion to temperature is an important diagnostic feature. To this we may add the playing of alae nasae and expiratory grunt.

The pelvic conditions which simulate appendicitis have been reviewed by Pratt.¹⁶⁴ The importance of tracing the course of the disease upward from the urethra, cervix and adenaxae by a careful history will be of value in distinguishing gonorrheal infections from appendicitis. With unruptured ectopic pregnancy the history of menstrual irregularity accompanied by vaginal bleeding is important. He has stressed the importance of distinguishing between the obstructive and inflammatory types of appendicitis in differentiating pain of pelvic origin.

Collins¹⁶⁵ stressed the importance of considering the possibility of mesenteric lymphadenitis when making a preoperative diagnosis of appendicitis in adolescents. He found this condition in 43 (2 per cent) of 2140 appendectomies, 26 (60.5 per cent) of these were in females. Season seemed important in his study, 37 cases (87.5 per cent) occurred between November and April, the greatest number in January. Throat culture taken in 39 cases showed *Streptococcus hemolyticus* in 37 (90.5 per cent). In the series, 35 (81.4 per cent) had a recent

sore throat or attack of tonsillitis. It was found important in the postoperative treatment to eliminate foci of infection in the nasopharynx to ensure a permanent cure.

Some interesting studies on lymphatic drainage from the ileocecal region were made by Klein.¹⁶⁶ By injecting 1 per cent indigo carmine into the subserosa of the lower part of the ileum (corresponding to the avascular space of Treves) he found the course was from left to right into the satellite nodes of the ileocecal region. The lymphatics of the appendix are not independent of those of the cecum, which has 2 sets, 1 emerging from the anterior wall and the other from the posterior wall, both run toward the ileocecal. A number of lymphatic glands are found in the ileocecal angle that drain the appendix, the cecum, and the lowermost small segment of ileum. These drain along the mesenteric artery, emptying into the chain near the third portion of the duodenum.

According to Klein, nonspecific mesenteric adenitis is divided into 3 types according to symptomatology. The first group is the least common and occurs in children from 6 to 12 years. The onset is sudden with high fever, marked toxemia, and a high blood count, the face is flushed, pulse rapid, and throat congested and inflamed. The abdomen is distended and tender throughout, especially in the right iliac fossa. When operated upon, the whole intestinal tract, particularly the small intestine, is thickened, extremely red, and the mesenteric glands are pink. The second type is most common and is often mistaken for appendicitis. However, the tender point in the right iliac fossa is at a higher level than in appendicitis and is internal to McBurney's point; and when the patient is turned on the left side the tender area is shifted to the left and is absent on the right. This

one sign when present has always differentiated mesenteric adenitis from appendicitis. The third type of mesenteric adenitis gives the same history as the second, but examination of the abdomen discloses that whereas the tenderness can be shifted from right to left by change of position, tenderness persists over the cecum. This type cannot always be differentiated from a pathological process which involves the appendix.

The differential diagnosis of acute abdominal syndromes should include *torsion of the great omentum* because this lesion occurs more frequently than is generally believed. Mauro¹⁶⁷ found that in 50 per cent of the cases it was confused with appendicitis. He reports 2 rare cases of intra-abdominal torsion of the great omentum complicated by acute appendicitis and intestinal volvulus.

In a review of 42 cases of torsion of the appendices epiploica, Fiske¹⁶⁸ found that appendicitis was the most frequent mistake in diagnosis. There was nothing characteristic in the pain unless the twisted appendix epiploicae was on the left side.

Appendicitis in Childhood.—As a result of the rapidity with which appendicitis develops, the difficulty in diagnosis, the short omentum, and other factors, appendicitis in childhood and infancy has carried a rather high mortality. For this reason numerous studies have recently been completed attempting to evaluate various types of treatment in these cases.

Deaver and Martin¹⁶⁹ studied 235 cases of acute appendicitis in children covering a 7-year period. The general mortality was 4.26 per cent and the mortality for children 5 years of age and under was 5.5 per cent. The last 4 years of the study shows a reduction in the mortality which corresponds to a clear-cut difference in the operative proce-

dures and postoperative treatment. In the entire series the mortality in perforation cases was reduced from 16.3 to 6.5 per cent, while the percentage of perforation cases remained unchanged. In children under 6 the mortality fell from 33.3 to 17.6 per cent. This mortality figure was obtained in the face of a greatly increased number of perforations, 85 per cent as compared with 46.2 per cent for the first period. The increasing use of the McBurney incision in preference to the right rectus incision was thought to be a factor responsible for this reduction in mortality. The appendix should always be removed, except in the localized abscess group. The only cases of peritonitis in which the appendix was not removed died, as was expected. Drainage was used only in the presence of gross septic or fecal contamination, or when exudate existed in the cecum, ileum or parietal peritoneum. When drains were used, they were used freely, a soft tube in the pelvis, 1 or 2 cigarette drains to the cecum and lateral gutter. Postoperative obstruction was minimized by placing a soft rubber cofferdam in such a position that the terminal ileum could not become adherent to the appendiceal bed. In 4 cases cecostomy through the appendiceal stump was done. Most patients were operated immediately after admission, however, in a few extremely ill cases the conservative treatment was tried for 12 hours, if improvement was noted it was continued, otherwise operation was performed. In the abscess group benefit was derived from expectant treatment and the extraperitoneal route of drainage was used if possible.

The postoperative complications are listed as: Intestinal obstruction, 4; fecal fistula, 1; transient fecal fistula, 3; secondary abscess, 2; wound infection, 6; pneumonia, 3; bronchitis, 2; otitis media, bilateral, 1; acute tonsillitis, 1; abscess,

1. The cause of death in 10 cases was: Peritonitis, 5; secondary abscess followed by peritonitis, 1; intestinal obstruction, 2; intestinal obstruction and peritonitis, 1; pneumonia, 1.

Adams and Bancroft¹⁷⁰ report the results of treating all cases of acute appendicitis in which there is evidence of perforation or extension by conservative means. Of 241 cases studied in children under 16 years, 110 were considered to have good evidence of extra-appendiceal extension when first seen. All cases of advanced peritonitis were included unless proven not to be of appendiceal origin. The treatment used may be briefly summarized. (1) Wangenstein drainage with x-ray checkup to locate the tube. (2) Flat in bed. (3) Hot applications in the form of stumps to the abdomen. (4) Codeine sulfate and phenobarbital to control restlessness. (5) Physiologic saline with 5 per cent dextrose by continuous intravenous drip, 90 to 100 cc per kg of body weight daily as long as continuous drainage was used, more fluids in summer or where vomiting or diarrhea had produced marked loss. In most cases response to treatment, *i.e.*, fall in temperature and pulse and improved general appearance, was noted in 48 hours.

In the 131 cases which were treated by immediate appendectomy there was 1 death due to anesthesia. In the other 110 cases treated conservatively there were 5 deaths, or a mortality of 4.5 per cent. In a group of 31 cases, 7 years and under, treated conservatively, there was only 1 death (3 per cent mortality). An interval appendectomy was done in 94 cases. There was little correlation between the operative findings and the microscopic pathological report. The most difficult cases at operation were reported to have an inactive appendix. However, 70 per cent of all the deferred appendectomies

had a report of acute appendicitis and 30 per cent inactive. The average duration of fever in the conservative cases was 9.2 days, and the average interval between the attack and the operation was 8.8 weeks; the average hospital stay after interval operation was 9.1 days. During the interval care 10 per cent, or 11 cases, had major exacerbations of symptoms. Certainly the general mortality rate of 2.49 per cent, and the mortality rate of 4.5 in complicated cases, warrants further observations on this type of treatment in the young children.

A series of 220 cases of acute appendicitis in childhood with 6 deaths have been reviewed by Caldwell.¹⁷¹ The general mortality was 2.7 per cent; of 210 cases in which the McBurney incision was used there were 4 deaths (mortality of 1.9 per cent), while there were 2 deaths in the 10 cases where a right rectus incision was used (mortality 20 per cent). Operation was done in all cases as soon as possible, getting the dehydration and acidosis controlled. The appendix was removed. *The importance of making the McBurney incision higher in children than in adults is stressed.* The reasons given are that rotation of the colon is more apt to be incomplete, hence the appendix higher, also the difficult appendices to remove are the retrocecal ones in which the tip is fixed at the level of the hepatic flexure. Simple ligation and carbolicization of the stump are sufficient. There was a tendency to use less drains, and only soft cigarette drains. Diffuse or localized peritonitis was not in itself considered an indication for drainage, the peritoneum was closed and the wound loosely packed. In 15 cases secondary pelvic abscess developed, but only 3 required surgical drainage.

Angel, *et al.*,¹⁷² report 104 cases of acute appendicitis in children under 13 years. Of these, 24 were 7 years or less,

the youngest was 3 years; 51 were females, 53 males. The incidence was higher in the months of May, June, July, and August. Thirty-nine had cathartics given by the family or the family physician. The average time elapsing before operation in the acute unruptured (69 cases, 0 deaths) was 2.3 days, the gangrenous unruptured (9 cases, 0 deaths) was 2.6 days; and the ruptured, including both with abscess and peritonitis (34 cases, 5 deaths, mortality 14.7 per cent) was 3.8 days. Operation was recommended in all cases. The McBurney incision was used in 102 cases; enterostomy was combined with appendectomy in 10 cases; colostomy in 1 case. The colostomy was done in a case of ruptured appendix associated with a sliding hernia. Although the general mortality in these cases was only 4.7 per cent, the complicated perforated cases had a mortality of 14.7 per cent, which is much higher than reported for the conservative method.

A series of 613 children treated for acute appendicitis and its complications were studied by Miller and Turner¹⁷³. They were divided into 3 clinical groups.

Group I—329 cases whose histories and physical findings revealed acute appendicitis before perforation. There was no mortality. All cases were operated immediately, unless the infection was in the subsiding stage.

Group II represents those cases showing localized inflammatory masses. These were cases of perforation in which the defense mechanism was considered adequate. Conservative treatment with interval appendectomy was considered the method of choice in treating these cases. Increase in the size and spread of the abscess were evident in a few cases, and extraperitoneal drainage was done with a low mortality rate.

Group III comprises those cases of acute perforation lacking an adequate defense mechanism. They represent, pathologically, the obstruction type of appendicitis with a perforation of considerable size. The findings are generalized rather than localized, while the acute general tenderness and rigidity suggest a rapidly spreading peritonitis. The authors feel that surgical removal of the source of infection, adequate drainage, cecostomy is the method of choice for treating these cases. In 163 cases in this group there was a mortality of 22.7 per cent.

According to McCarthy and McGrath,¹⁷⁴ there are only 17 reported cases which have been operated upon for acute appendicitis alone in infants less than 1 year. This figure does not include a far greater number of cases in which the appendix was found in inguinal hernias that have become strangulated or incarcerated. They report the case of an infant 8 months from whom a gangrenous appendix perforated by a fecalith was removed. One pint of yellow pus was aspirated from the peritoneal cavity. Recovery followed. They state that flexion of the right thigh on gentle palpation is a valuable sign if the child's attention is elsewhere occupied.

Campbell¹⁷⁵ reports a case of acute perforative appendicitis in a child 2 months old. The perforation occurred in a hernial sac. Operation was followed by recovery.

Treatment—It is more or less generally conceded that *immediate operation* is the treatment of choice for acute appendicitis before perforation and peritonitis have developed. For the advanced pathological state, there is a division of thought; some feel that conservative or *Ochsner treatment* should be followed awaiting localization or resolution, while others feel that an immediate appendec-

tomy should be done. Some form of **serum therapy** may be advantageous, although it is not generally used in this country. The question of **surgical drainage** of abscesses *versus* delay awaiting absorption is also controversial at the present time

Immediate Operation—On the basis of 929 cases with a mortality of 12 per cent over a period of 3 years (1930-1933), Margottini¹⁷⁶ advocates immediate operation in every stage of the process, at any time, day or night, barring special general considerations. The statistical material comprises (a) 748 cases of acute appendicitis with a mortality of 0.13 per cent. (b) 87 cases of circumscribed peritonitis with mortality of 2.3 per cent, and (c) 94 cases of diffuse peritonitis with mortality of 8.6 per cent. He feels that immediate intervention in acute appendicitis not only reduces the mortality, but is also the best means of preventing complications, especially peritonitis. If circumscribed peritonitis is already present, intervention prevents its diffusion and in diffuse peritonitis it is the only means of preventing ileus. The material is homogeneous in that certain principles were followed, except in the uncomplicated acute and a very few peritonitis cases, immediate operation, drainage, removal of the appendix and burial of the stump wherever possible.

Spinal anesthesia was the anesthetic of choice, except in a few cases of peritonitis where local was employed. Ether was used for children under 16 years. A McBurney incision was used in all cases. The appendix was removed in all but 4 cases, 3 large abscesses, and 1 case in precarious general conditions. Drainage *a la* Mikulicz was used, adapting the number and size of the drains to the case. The abdominal wound was closed loosely or not at all. When the wall was closed

without drainage, the peritoneal cavity was lavaged with colloidal silver. In a few cases of ichorous peritonitis anti-gangrenous serum was used to advantage, locally as well as by intramuscular injection.

Horsley¹⁷⁷ is strongly in favor of immediate operation, and removal of the appendix in every case of acute appendicitis, abscess or not. He reports 494 cases of acute appendicitis with 3 deaths (0.607 per cent), 100 cases of acute appendicitis with peritonitis with 2 deaths (2 per cent), giving total mortality of 0.842 per cent excluding the chronic and subacute cases. In no case did they fail to remove the appendix. The routine procedures at his clinic are

1 **Immediate operation** for acute appendicitis, as soon as the diagnosis is made, no matter what the stage of the disease.

2 **McBurney incision**, gentle handling of the tissues and always removal of the appendix. Removal of the appendix obviously saves morbidity, and hospital expense, and reduces mortality rate.

3 **Suction apparatus** instead of sponging. Sponging presses sepsis into the areolar tissue. This is a very important point on technique. If you sponge the pus out with a gauze on a sponge holder, you get out some pus but you also massage some of it into the retroperitoneal tissues.

4 **Physiologic rest of the affected colon and cecum**, by avoiding proctoclysis and by administering intravenous dextrose or dextrose in salt solution, and using Jutte tube or Levine tube into the stomach, also using a minimum of drainage. Proctoclysis defeats the purpose, since it not only distends the colon and cecum, tends to create peristalsis, but, because the right side of the colon is the chief absorptive area, it puts additional stress at the inflamed site.

TABLE X

SHOWING THE RELATIONSHIP OF TYPE OF APPENDICECTOMY INCISION AND THE MORTALITY

Type of Incision	Local Peritonitis		Generalized Peritonitis		Appendiceal Abscess		General Peritonitis and Abscess		Total Cases	Total Mortality
	Cases	Deaths	Cases	Deaths	Cases	Deaths	Cases	Deaths		
Gridiron or McBurney	40 (72.7%)	0	41 (65.0%)	6 (15.0%)	85 (72.6%)	3 (3.5%)	9 (3.5%)	2 (22.0%)	175 (70.0%)	11 (6.2%)
Right Rectus	13 (23.6%)	0	19 (30.1%)	6 (31.6%)	25 (21.3%)	1 (4.0%)	6 (40.0%)	5 (83.3%)	63 (25.2%)	12 (19.4%)
"Midline" Suprapubic	2 (4.4%)	0	3 (4.7%)	2 (66.0%)	6 (5.1%)	1 (16.6%)	0	0	11 (4.4%)	3 (27.2%)
Hermiotomy (mistaken diagnosis)	0	0	0	0	0	0	0	0	1 (4%)	0
Totals	55	0	63	14	117	5	15	7	250 (100%)	23

Note Two cases of general peritonitis in extremis were not operated upon.

(Courtesy, Annals of Surgery, May, 1937)

5 *Simple treatment of the stumps of the appendix*, merely ligating and bringing a tag of peritoneum covered fat to protect the stump from the drainage tube.

In a study of 252 consecutive cases of acute perforated appendicitis, McClure and Altmeier¹⁷⁸ report a mortality of 0 per cent for 55 cases of early perforation with local peritonitis, 42 per cent for 117 cases complicated by circumscribed abscess, 21.5 per cent for 65 cases of acute spreading or generalized peritonitis, and 46.6 per cent for 15 cases of both acute generalized peritonitis and abscess formation. The total mortality for this series was 10.4 per cent. All cases were operated immediately after the diagnosis of acute appendicitis was made regardless of the duration of the symptoms, unless the patient was moribund. Intravenous *glucose* and *saline* was used, preoperatively as required. The appendix was removed in every instance where it was felt that the patient's condition would stand it. *Ligation* and *inversion of the stump* was done in all but 31 cases (23 abscess—2 deaths, 4 local peritonitis, 2 abscesses and general peritonitis—2 deaths) where simple ligation was done. In 19 cases the appendix

was not removed: 17 abscess—1 death; 2 general peritonitis—2 deaths. They state that the mortality rate in the patients in whom the appendix was not removed was 15.8 per cent compared to 9.99 per cent for the cases in which it was removed, and the patients in whom it was not removed were much more ill. All cases were drained with 1 to 3 cigarette drains, usually through the original incision.

A comparison of the mortality rate in relation to the type of incision used is of value, Table X. Although the series is small, it shows rather conclusively, as do other statistics, that the McBurney incision is the incision of choice in acute appendicitis, ruptured or unruptured, and at any age.

Nassau¹⁷⁹ is in accord that all early cases demand immediate operation with removal of the appendix if safe and possible to do so. When the appendix forms part of the abscess wall, it must be determined if it can be removed without breaking into the peritoneal cavity. If there is much infection simple ligation of the stump is all that is necessary. Purse-string sutures in the thickened inflamed cecum may cause sloughing. The wound is to be left completely open in all badly

infected cases. Drains should be accurately placed. A dressed tube into the bottom of the pelvis, plain or iodoform gauze is used to keep the tube in place and the wound open.

His *postoperative treatment* is the same as advocated by most men, *i. e.*, **morphine** for comfort, **liquids by mouth** after restoration of bowel tone, **Wangensteen drainage, continuous intravenous glucose solution, hypodermoclysis, blood transfusions.**

However, Nassau feels that in a small group of cases of ruptured appendicitis delay in operation is a wiser and safer procedure. In these cases the Ochsner treatment is used for localization and the abscess is drained at a later date. In a recent survey, localization of the abscess in the pelvis occurred in 18 cases; incision and drainage by rectum resulted in 17 recoveries and 1 death.

Kennedy¹⁸⁰ takes a very radical stand in regards to the treatment of the peritonitic abdomen. He operates during the first hour, irrespective of time or extent of involvement, doing radical surgery, removing the distal infecting source, exposing the full extent of the peritonitic area by intestinal evisceration, breaking up adhesions and flushing the abdomens in those cases of diffuse peritonitis that have a great amount of pus. He does not flush any abdomen that is not diffusely peritonitic and demonstrated as such except the frank perforations. No drain other than the coffer dam gauze is used, and it is used with the idea of physical mechanics. He takes the position that it is the complications of peritonitis, namely, partial or complete intestinal obstruction, distal abscess, and retroperitoneal infections, which are the causes of the final and fatal dose of toxins and not the peritonitis. He states, "The death rate from postoperative complications incident to feeble primary surgery is much

greater than would have been the outcome if no surgery had been done."

Delayed Operation—In current literature, many surgeons are practicing and advocating the delayed or *Ochsner type of treatment* for the cases of perforated appendicitis and its complications. The rationale of this treatment is based upon the fact that a natural protective mechanism exists within the abdomen which, if left undisturbed, will usually result in resolution or localization of the appendiceal peritonitis.

Bower¹⁸¹ has stressed the responsibility of the members of the surgical staff, from the chief, associates and interne's standpoint. He feels that spreading peritonitis complicating appendicitis requires a preoperative consultation with the chief and a recording of the findings as well as the opinion of the chief. With proper co-operation of all members, the mortality of this serious condition may be reduced. In a study of mortality statistics from 2573 cases of spreading peritonitis due to a perforated appendix arranged in 24-hour groups, it was found that the mortality rate increases with each 24 hours up to the fifth day, then there is a slight decline on the sixth day, followed by a marked drop on the seventh day. It is suggested that immunity plays a role in the recovery of these patients. In a study of 31 cases operated upon, 61.05 hours after the onset of the symptoms, there was a mortality rate of 19.35 per cent; while in a series of 35 cases operated upon 184.8 hours after the onset of symptoms, there was a mortality of 5.71 per cent. Both of these groups received perfringens antitoxin.

According to Gardner,¹⁸² "the delayed form of operative treatment in appendiceal peritonitis is based on sound physiologic and surgical principles. It is indicated in all forms of appendiceal peritonitis regardless of age except in the

TABLE XI
INCIDENCE OF CHOICE OF THERAPEUTIC PROCEDURE BY YEARS

Year	Group I Simple Acute Appendicitis	Group II Abscess					Group III Diffuse Peritonitis				
		Immediate Operation		Conservative Treatment Begun			Immediate Operation		Conservative Treatment Begun		
	Operation			No Opera- tion	Operation				No Opera- tion		
	Forced	Elec- tive	Elec- tive		Forced	Forced	Elec- tive	Elec- tive		Forced	
1933.	202	2	39	3	2	0	0	9	4	2	1
1934	128	0	25	7	1	3	0	6	1	3	1
1935	164	0	23	3	3	3	0	4	1	3	0
1936	148	0	8	1	6	22	0	4	0	5	3
1937	187	1	3	1	5	20	0	7	0	4	1
Totals	829	3	98	15	17	48	0	30	6	17	6

(Courtesy, Annals of Surgery, November, 1938)

presence of early perforation with wide-spread signs of peritonitis. Management of the treatment requires *absolute rest of the intestinal tract*, maintenance of an *adequate fluid, mineral, and colon intake* by routes other than the intestinal tract, and careful observation for evidence of continued spread of a peritonitis or rupture of an abscess, in which case immediate operation becomes necessary." The selection of cases for delayed or immediate operation are dependent upon individual evaluation, history, physical and laboratory findings, time while arbitrarily set at 48 hours after the onset of symptoms cannot be used in all cases. If after careful evaluation of all diagnostic methods there exists doubt as to whether the appendix has ruptured or not, an immediate operation is done. The practice of immediate operation on all children has proven unsatisfactory, in the future conservative therapy will be tried.

A comparison of 2 groups of patients treated at different times shows a definite improvement in mortality rate by delayed treatment. In a series of 122 patients observed from 1930-1934, when delayed operation was used only occasionally, the mortality rate was 18 per cent. From

1934 to 1937, when 126 cases were treated, delayed operation being used in all cases when indicated, there was a mortality rate of 8.7 per cent. The reduction was accomplished mainly in the local peritonitis and abscess cases. The mortality dropped from 10 per cent to 5 per cent and from 14.3 per cent to 4.2 per cent respectively in these patients. He attributes the failure of reducing the mortality in the general peritonitis group to the fact that all children with diffuse peritonitis were treated by immediate operation in both series.

The complication incidence in survivors of delayed operation was 5 per cent and of immediate operation 20 per cent. The average period of hospitalization under the conservative régime was 16 days, and in the immediate operation group 26 days.

Gardner summarizes by stating, "The reduction in mortality, incidence of complication, and duration of hospitalization in patients with appendiceal peritonitis treated by delayed operation justifies the more widely accepted use of this form of treatment."

Analyzing 1069 cases of acute appendicitis during a 5-year period (1933-

TABLE XII
MORTALITY AND MORBIDITY FOLLOWING VARIOUS THERAPEUTIC PROCEDURES

	Immediate Operation		Conservative Treatment Begun		
	Forced	Elective	Operation		No Operation
			Elective	Forced	
Data on Total Cases					
Number of Cases	3	98	15	17	48
Complications per Patient	1 66	0 63	0 60	0 94	0
Deaths	1	4	3	1	0
Mortality	33 3%	4 0%	20.0%	5 9%	0 0%
Data on Living Cases					
Number of Cases	2	94	12	16	48
Average Days in Hospital	32	19 5	30 6	27 8	11 9
Average Days of Fever	29	17 7	25 2	25 8	9
Per Cent of Cases Discharged with Fever	0 0	46 9	16 6	56 0	31 2
Average Days of Drainage Known	28 5	20 1	22 2	41 3	0
Per Cent of Cases in Which Date of Termination of Drainage Is Unknown	50 0	76 5	58 3	75 0	0.0

(Courtesy, *Annals of Surgery*, November 1938.)

1937), Lehman and Parker¹⁸³ found that the infection had spread beyond the appendix in 240 cases, of these 181 were diagnosed as intraperitoneal abscess. The cases have been tabulated under 5 programs of treatment in cases of extraperitoneal involvement

(1) Immediate Operation Forced—Cases are included under this heading in which immediate operation was decided upon, not because of the stage of the abscess or the accepted current practice, but because of unmistakable indications for surgical intervention (2) Immediate operation Elective operations were performed, on the basis of what were considered established surgical principles. In the abscess group they represent cases presenting well-localized masses of some days' standing (3) Conservative treatment begun. Operation Elective—In this group are included cases presenting marked sepsis and evidence of incomplete localization of abscess, which, after a few days of conservative treatment, showed dimin-

ished sepsis and a sharply localized mass and were then operated upon as a matter of principle (4) Conservative treatment begun Operation Forced—This group includes cases presenting on admission evidence of either a well-localized or a poorly localized abscess. Under conservative treatment the course of the disease took an unfavorable direction, and operation seemed indicated on unquestioned surgical principles. These indications included acute intestinal obstruction, growth in size of the abscess, and threatened perforation of an abscess into the abdominal wall or the rectum, usually accompanied by increasing signs of sepsis (5) Conservative treatment begun No operation—The cases in this group fulfill the requirements for the diagnosis of abscess or diffuse peritonitis and in none was operation performed before discharge. The change in preferential method of treating abscess, from immediate operation in well-localized cases or elective, delayed operation in those poorly localized, to nonoperative

TABLE XIII

RESULTS FOLLOWING THE INITIATION OF CONSERVATIVE TREATMENT WITH SUCCESSFUL AND UNSUCCESSFUL GROUPS COMBINED, AS COMPARED TO RESULTS FOLLOWING ALL ELECTIVE OPERATIONS

	Conservative Treatment. No Operation and Operation Forced (Combined Columns 4 and 5, Table)	Elective Operation. Immediate and Late Combined Columns(2 and 3, Table)
Data on Total Cases		
Number of Cases	65	113
Complications per Patient	0.25	0.63
Deaths	1	7
Mortality	1.5%	6.2%
Data on Living Cases		
Number of Cases	64	106
Average Days in Hospital	15.8	10.7
Average Days of Fever	13.2	15.9
Per Cent of Cases Discharged with Fever	37.5	45.3
Average Days of Drainage Known	10.3	20.3
Per Cent of Cases in Which Date of Termination of Drainage Is Unknown	18.7	83.9

(Courtesy, Annals of Surgery, November, 1938)

treatment in all cases if possible, forms the chief basis of comparison in this study (Table XI). It is seen that during the years 1933-1935, only 22.3 per cent of abscess cases were treated by conservative measures and only 6 per cent were carried through without operation. By contrast, in the years 1936-37 in 83.3 per cent of the abscesses conservative treatment was started and 65 per cent were carried through without operation. Throughout the 5-year period the preferred immediate treatment was nonoperative in diffuse peritonitis, and deviations have been the result of diagnostic difficulties. The mortality and morbidity following the various therapeutic procedures are best seen in Table XII.

A complete estimation of the results of the conservative must compare the combined results of successful and unsuccessful conservative with those of all elective operations. Such a comparison (Table XIII) reveals that the elective

group suffers over twice as many complications as the combined nonoperative and forced delayed operative groups, remains in the hospital about one-third more days, is febrile almost 25 per cent longer, and drains practically twice as long. The fact that the mortality is over 4 times as great in the elective group as in the conservative group must not be accepted too confidently, since the ratio of difference to standard error is just below 2. Care is essential in using the conservative treatment in children and old people. Although the percentage of patients who returned for an interval appendectomy was small for both the surgically drained abscess and the non-surgical drainage, there was no mortality and the average hospital stay was 8.1 days.

Coller in discussing this paper states that for 10 years they have practiced conservative treatment for the peritonitis group, operating only if the patient does not improve or if an abscess develops

During the past 3 years the patients with abscess have been observed for a longer time before operation. He feels that distinction must be made between the appendiceal abscess and the large pelvic collections which develop after the conservative treatment of the diffuse peritonitis group, in the latter surgical drainage is indicated.

The same conservative treatment of right lower abdominal masses has been practiced for 3 years by Orr. Drainage was done only for full-blown abscess. About 50 per cent of the cases got well and went home without operation. He feels that distention is the crux of the situation in distinguishing between the type of therapy to use. Those cases in which the disease is confined to the appendix and those that have ruptured and have no distention are operated at once. Those with masses and those with distention due to peritonitis are treated conservatively.

Graham states that their management coincides with that outlined by Lehman and Parker, and about 60 per cent of the cases were discharged without operation. He advises surgical drainage for the full-blown abscess.

The conservative treatment of appendiceal abscess has been followed by Wangenstein since 1931. He is cautious concerning the prolonged treatment of abscesses which continue to be large. The danger being intraperitoneal rupture and hemorrhage from erosion of large blood vessels by the abscess. The subsidence of fever and decrease in the size of the abscess are signs which indicate that it is safe to pursue a conservative régime.

The dangerous effect of teaching conservative therapy and its influence upon the general practitioner has been emphasized by Whipple and Lilienthal.

Serum Therapy—Altenkamp¹⁸⁴ has treated cases of perforated appendicitis

by an antitoxic and antibacterial cattle serum manufactured by Sachsische, Serumwerke, Doesden. An initial dose of 50 cc., one-half intraperitoneal and one-half intramuscular, is given at the operation. An original dose of 75 cc. or more may be used in severe cases, and the original dose may be repeated on days following the operation by either or both routes. Appendectomy to remove the source of infection was done in all cases. Besides the reduction in mortality and the duration of the disease, there has been a marked improvement in the post-operative appearance and action of the patient. Comparative studies on similar cases in the years 1930-1932 showed 299 cases of acute appendicitis with 55 perforations and 16 deaths, while in the years 1934 to 1936, when serum was used, there were 393 cases of acute appendicitis with 66 perforations and only 4 deaths. Anaphylactic reactions were not encountered, erythemas were noted on the seventh day but not considered significant.

According to Lagiader¹⁸⁵ the experiences with peritonitis serum in general have been favorable. In the 8 years between 1928 and 1935, 135 of 817 patients with appendicitis had perforations and showed beginning or far advanced peritonitis, 27 (20 per cent) of these died. From 1936 to 1937, 214 were operated upon, 49 had perforations and only 2 (4 per cent) died. One of these was a 78-year-old man who died of marasmus 4 weeks after the operation. He usually gives 3 doses of 25 cc. for 2 or 3 days; the first dose being intraperitoneal and subsequent doses intramuscular. Only in very severe cases are 6 injections given. He noticed rapid objective and subjective improvement in the postoperative course. The serum of the Swiss Serum Institute is preferred as it is a bovine serum and is mixed

with serum antagnotic to the colon bacillus and the gas bacillus.

In this country, Bower¹⁸¹ has been interested in the use of perfringens antitoxin in the treatment of perforated appendix with spreading peritonitis. Believing that patients who recover from peritonitis develop antibodies in their sera, they have studied cases treated with lyophilized convalescent serum. The results are to be published.

Drainage—Babcock¹⁸⁶ has stressed the inefficiency of abdominal drainage, the possibility of pelvic drains fixing infection in the pelvis leading to secondary pelvic abscess, the danger of drains between intestinal coils; the indications for gauze drains with the danger of too early and too late removal of these drains, and the possible allergic reactions in certain individuals to rubber and iodoform. He has used large caliber (2 to 8 cm.) glass tubes of varying lengths for 2-stage drainage of the gall bladder and appendiceal abscesses. With the appendiceal abscess, which cannot be drained laterally or extraperitoneally, a glass tube is anchored to it with several fine alloy steel wire sutures, walling off is awaited, and drainage of the abscess by cautery under direct vision through the glass tube is accomplished.

For perforated or septic appendix with diffuse peritonitis, the operation should be brief, with minimal intra-abdominal manipulation. Additional contamination from the appendix should be prevented and, if pus in the peritoneal cavity is badly contaminated, prolonged peritoneal drainage is desirable. In a small series of cases he used the following procedure without a mortality. The abdomen is opened through a muscle-splitting incision at McBurney's point or over the point of mass or greatest rigidity. A curved hemostat is passed through a glass tube 2 to 4 cm. in diameter and

clamped across the base of the appendix and mesoappendix. The glass tube is caused to slide over the appendix to contact with the cecum. No other drains are used. The general peritoneal cavity is drained through 4 small openings near the end of the glass tube. The clamp anchors the glass drain, and 3 or 4 days later the appendix is removed by a tonsil snare or curved scissors. The clamp is then removed. In 2 or 3 days the glass tube may be removed, and the muscles allowed to fall together. An alternative procedure requiring more manipulation is to ligate and divide the base of appendix and mesoappendix, amputate the appendix and tie the ends of the 2 ligatures through the openings on opposite sides of outer border of the glass tube with sufficient tension to anchor the tube against the cecum. Unless properly anchored to the cecum, loops of small bowel may herniate into the tube producing obstruction.

Mulleder¹⁸⁷ calls attention to the fact that an improvement in the result of the treatment of appendicitis may be achieved by primary closure of the abdominal wall. He was able to reduce his mortality from 3.2 to 0.83 per cent. If an abscess develops in the *cul-de-sac* after operation it must be drained, but primary drainage does not prevent these pelvic abscesses. He used drainage in children and old people, in cases with fibrin and foul exudate. He believes that the primary closure of abdominal wound has not only reduced mortality, but also reduced complications and postoperative symptoms.

After obtaining encouraging results in the treatment of about 25 cases of appendiceal peritonitis by eliminating the focus and closing the peritoneum, leaving a drain only to the closed peritoneum, Cafritz¹⁸⁸ set down the following rules concerning drainage. Drainage of appen-

diceal peritonitis is indicated (a) in cases in which the primary focus cannot be removed; (b) in cases in which a large amount of necrotic and contaminated tissue is left in the abdominal cavity, and (c) in cases of walled-off abscess. In all other cases it is definitely contraindicated.

Connell,¹⁸⁹ feeling that death in cases of perforated appendicitis is due to an ileus, rather than peritonitis, has advocated enterostomy in addition to appen-

toneal cavity; (b) silk is preferable to catgut as a purse-string suture although a final conclusion was not reached. The danger of perforating the cecal wall with the suture, the contamination of the needle and suture passing through the wall, the possibility of abscess within the cecal wall due to invagination are all considered in this paper.

In the discussion, Horsley points out that the variation of the anatomy of the appendix in a dog as compared to that

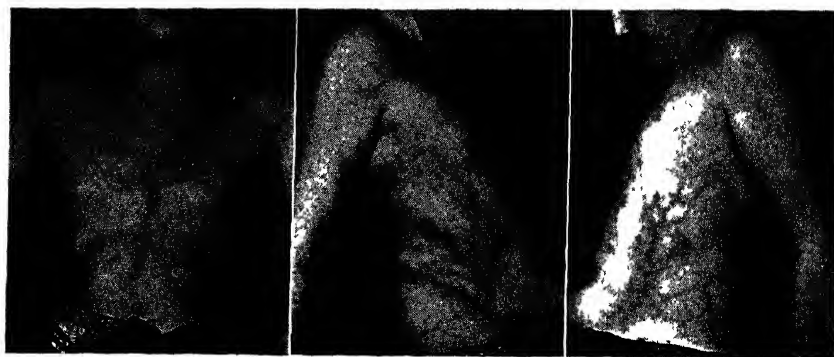


Fig. 4—Enlargement of superficial veins. Photograph made with the infrared technique. (Courtesy, Proceedings of the Staff Meetings of the Mayo Clinic, Dec. 22, 1937.)

dectomy. The recent records, 1934 to 1938, show 8 deaths in 56 cases (14.2 per cent treated by enterostomy, as compared with a similar series of 38 cases without enterostomy with 13 deaths (34.2 per cent). The evidence presented in these groups is not very convincing. Enterostomy has been advocated for many years.

Technic of Appendectomy—After considerable favorable clinical experience with the noninvagination technic, Donaldson and Thatcher¹⁹⁰ set out to prove experimentally that this was the best technic for appendectomy. From experimental data obtained by operating on 82 dogs they conclude (a) Ligation of the stump followed by invagination with fine black silk is preferable to ligation and leaving the stump free in the peri-

toneal cavity. He does not feel that the author is justified in changing a successful technic for a more difficult one on the basis of these experiments. He brings out an important point in the simple ligation method which he employs. Since crushing the stump produces much more trauma than simple tight ligation which cuts the mucosa clean and allows better healing, he advises simple ligation only.

The technic of inversion without ligation has been adequately reviewed in the last revision service of the *Cyclopedia*.

Thrombophlebitis—According to Hawkes¹⁹¹ the occurrence of thrombophlebitis of the appendiceal vein so alters the diagnostic, prognostic and therapeutic features of the disease that it seems

justifiable to place it in a category of its own. From a clinical standpoint, chills associated with other symptoms and signs of appendicitis should lead to the diagnosis of this condition. He quotes from Deaver in 1900, "Chills are a rather uncommon occurrence in appen-

are not rare with severe lesions. Of the patients with acute appendicitis not associated with abscess or general peritonitis admitted to Johns Hopkins Hospital, 15 per cent of these gave a history of chills and in all of them with the exception of 2 the appendix was gangrenous, per-



Fig 5—Lipiodol injection of the sinus tract in Case 1 The sinus tract extends downward and inward toward the pelvis and opaque material enters the rectal pouch near its proximal portion (Surgery, Sept., 1938)

dicitis, yet if at the onset of the attack they occur in rapid succession, and are accompanied by temperature, they indicate a rapidly developing gangrene of the appendix—chills occurring on the second or third day of the attack and associated with high fever usually indicate the development of metastatic or embolic abscess" Kelly writing in 1905 is quoted: "Chills are exceptional in cases of simple diffuse inflammation, but

forated, or distended with pus. Repeated chills occurring later in the course of the malady generally indicate a dissemination of the pyemic process."

He presents case histories of 16 proven and 8 presumptive cases of thrombophlebitis of the appendiceal vein. The importance of early diagnosis and treatment is emphasized. The treatment consists of ligation of the ileocolic vein above the thrombus before appendec-

tomy is performed. Unless early ligation of the ileocolic vein is done, emboli may occur, causing either pyelphlebitis or liver abscess. It is believed that early recognition and proper treatment of this type may contribute to a lowering of

case of thrombophlebitis occurring first in the left leg on the ninth day after the removal of a gangrenous appendix; then on the fifteenth day the right leg became involved, indicating a spread of the thrombus to the iliac bifurcation and



Fig 6—Lipiodol injection of the sinus tract in Case 2. After an injection of lipiodol through a catheter, the sinus tract is seen to extend posteriorly and medially. It is about 6 cm in length and communicates with a rather large abscess cavity measuring about 4 by 3 cm (Surgery, Sept., 1938.)

the mortality rate of appendicitis as a whole.

Ward and Horton¹⁹² state that thrombophlebitis of the great saphenous, femoral, and iliac veins complicates 1 to 2 per cent of all abdominal operations, but that its occurrence in children is extremely rare. They report an unusual

inferior vena cava. During a 4-month observation period the superficial veins of the anterior and lateral abdominal wall and thorax became very prominent as a result of the establishment of collateral circulation. An infrared photograph shows the enlargement of the superficial veins (Fig 4)

Complications—Fecal fistulae following appendectomy are much less common now than previously. Usually they heal spontaneously and in those which do not fecaliths, foreign bodies, terminal ileitis, actinomycosis, tuberculosis should be suspected.

Mendelsohn and Schriver¹⁹³ state that the operative treatment is hazardous, while conservative treatment frequently

fistula following appendectomy. The fistula failed to close after operation and 8 months later it closed within 10 days after injection with lipiodol (Figs. 5 and 6).

Appendicitis and Urology—Strominger¹⁹⁴ feels that too many cases of right lower quadrant pain have an appendectomy without a sufficient diagnostic study. Unless symptoms are severe

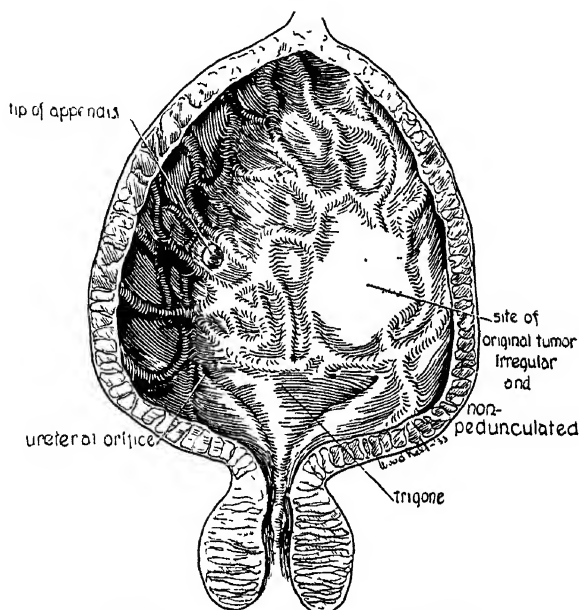


Diagram of bladder showing relationship of tumor to tip of appendix

Fig 7

(Courtesy, Am J Surg)

meets with stubborn failure to heal. Where the patient is a poor surgical risk, or where there is danger of contamination in surgical intervention, the only course is conservative treatment and the outlook often pessimistic. On the basis of 2 cases treated with lipiodol injected into the fistulous tract, they advise its use in other cases.

The first case was a white woman of 65 years who had a fecal fistula of 3 months' duration which healed within 1 week after the injection of lipiodol to outline the tract. Case 2 was a 55-year-old woman who had an operation 3 months after the development of a fecal

and definitely indicative of appendicitis these cases should have a careful urologic examination. Often evidence of latent infection of the kidney will be found, a pyuria or a microscopic hematuria; sometimes hydronephrosis, ureteral calculus or pyelitis will be discovered in this way. Often the author has been called in consultation after an appendectomy because of urological symptoms and found a ureteral calculus, a ureteral obstruction, pyelitis or pyelonephritis and sometimes even a urinary tract infection or obstruction on the left side producing reflex pain on the right. In other cases the urinary tract infection

may be secondary to the appendicitis. Albuminuria or hematuria may result from toxemia which may be caused by a general colon bacillus infection or the toxins from the infected appendix alone.

After a short review of the associated anatomy and physiopathology of the ap-

In 1402 consecutive, unselected, emergency appendectomies for proven appendicitis, Collins¹⁹⁶ encountered hematuria due to appendicitis in 124 patients, an incidence of 8.84 per cent. Due to a 4-hour delay in excluding genitourinary disease as the cause of hematuria, he

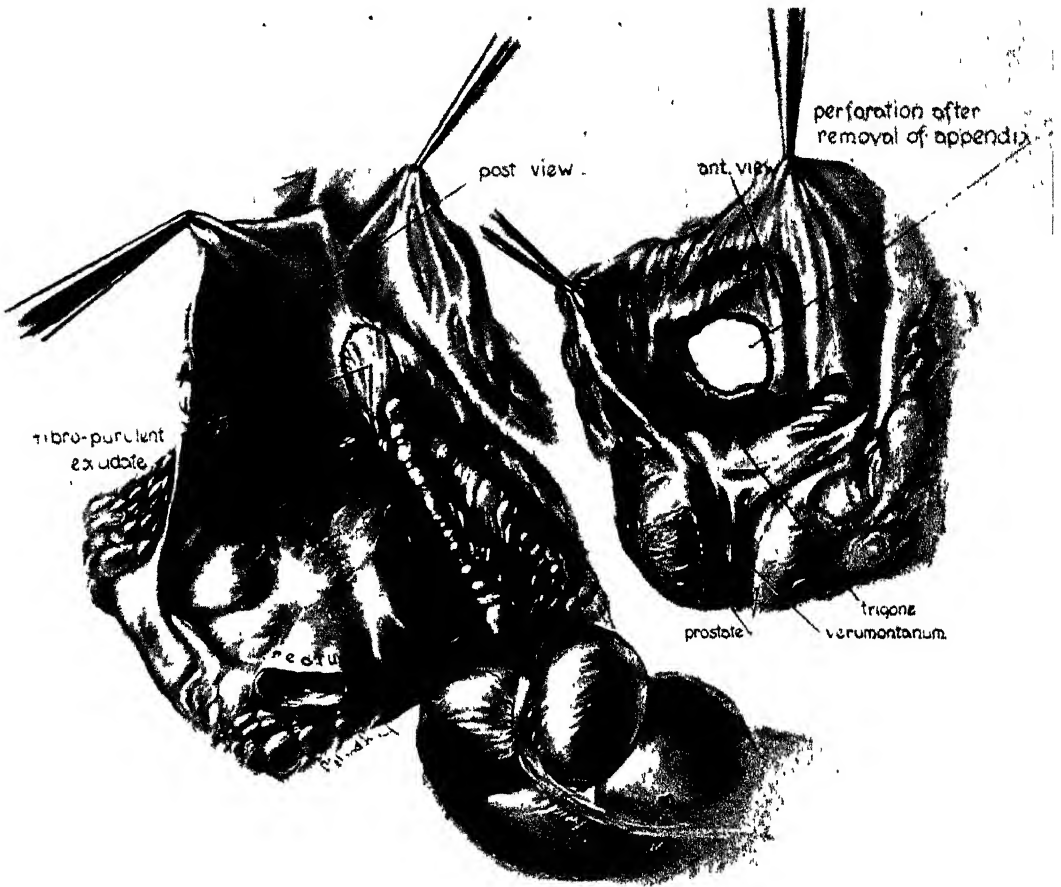


Fig 8—Anterior and posterior views of autopsy specimen, bringing out relationship of the various organs involved (Courtesy, *Am J Surg*, July, 1938)

pendix and the urinary tract on the right side, Donati¹⁹⁵ discloses the relative frequency of urinary symptoms as well as urinary findings elicited during an attack of both acute and chronic appendicitis. In his experience a great many patients with urinary symptoms, pain and hematuria, from an anomaly on the right side of the urinary tract associated with appendicitis, were definitely relieved of such symptoms by appendectomy.

found the mortality was increased from 4.7 per cent to 6.2 per cent. In about 84 per cent of the cases the appendix was fixed in the retrocecal position. The hematuria disappeared on an average by the fourth postoperative day, but the extremes varied from the first to the twenty-second day after operation. Hematuria due to appendicitis is a diagnosis which can only be made by exercising extreme care and an accurate and skilled

preoperative study of the genitourinary tract, including cystoscopy.

According to Blachley¹⁹⁷ the occurrence of genitourinary symptoms is rather common, and important to the surgeon for the reason that they may cloud the issue. Vesical, renal and testicular complaints are noted, and while these may be of reflex origin, in many instances, the most common cause is appendicular inflammation causing a pericystitis or cystitis of which the early manifestations noted on the second and third day are painful micturation, tenesmus, retention. When this occurs, the appendix is situated in the pelvis, in contact with the bladder. Right-sided pain and swelling of the epididymus and testicle have been noted when the suppurative appendix lies in contact with the area about the internal ring, the infection reaching these organs either by way of the blood vessels or lymphatics. He reports 2 interesting cases with testicular swelling and pain, which at operation were found to have acute appendicitis, 1 around the internal abdominal ring, the other pointing below Poupart's ligament. One had previously been considered a case of gonorrheal epididymitis.

Goldstein¹⁹⁸ presented a very unusual case of rupture of the bladder caused by fulguration of a protruding intravesical appendix (Fig 7). This patient, a man of 59 years, had painless hematuria of 2 months' duration, with anorexia, constipation, and a loss of 25 pounds in a few months. He was found to have a tumor of the bladder which disappeared after several fulguration treatments. Following the treatments he had severe abdominal pain and constipation. During his last cystoscopic examination a protrusion was noted; this was fulgurated and immediately followed by severe abdominal pain and syncope. Although a perforated bladder could not be demon-

strated by a fluid test of the bladder capacity it was suspected. The patient died 70 hours after the fulguration, and 9 hours after an abdominal operation. The operative findings were a low pelvic appendix adherent to the bladder with fibropurulent exudate covering the cecum and ileum. An ileostomy was done for an accidental perforation of the ileum. The most interesting autopsy finding was an appendix which was injected and adherent to the bladder by a thick green mass of exudate. When it was pulled away from the bladder it left an opening in the bladder wall $\frac{1}{5}$ cm in diameter (Fig 8).

Wound infections are not uncommon complications of appendectomies, but Sullivan¹⁹⁹ reported an unusual type of infection. A woman who gave a history of acute appendicitis, and later a true history of gonorrheal infection, developed a wound infection 7 days after a laparotomy with appendectomy. This infection was proven to be due to the gonococcus by culture and smears. Perhaps with proper culture media we would find this type of infection more common than we realize.

Appendicitis and Female Sterility—Von Mikulicz-Radecki²⁰⁰ found that in 14 per cent of sterile women appendicitis is the cause of sterility by way of the tube and ovaries. As regards frequency, appendicitis takes third place among the causes of sterility, it is surpassed by inflammations of the genitalia and hormone disturbances. Sterile women in whom tubal or ovarian changes exist should be investigated from the standpoint of appendectomy and appendiceal attacks. If an operation is done for sterility, the appendix should be carefully investigated as a source of infection. He opposes conservative therapy on the basis of possible damage to the genitalia.

INTESTINES

By DANIEL J. PRESTON, M.D.

Intestinal Obstruction

Etiology—Interruption of the normal passage of intestinal contents through the lumen of the bowel results from a variety of causes which may be grouped into 4 main classes.

1. *Intrinsic Causes* Obstruction to the fecal current arises from disease in the wall of the intestine (tumors, congenital atresia) which encroaches upon the lumen.

2. *Extrinsic Causes.* Abnormalities outside the bowel wall cause compression of the lumen by their contiguity to the intestines (tumors, hernia) Masses of foreign matter within the lumen interrupt the fecal current (bezoar, gall-stone) and bacterial action causes inflammatory ileus (peritonitis)

3 *Neurogenic Causes.* Interference with conduction of impulses by the autonomic nervous system produces dystonia of the intestine (trauma, tabes, drugs, Hirschsprung's disease)

4 *Vascular Causes* Thrombosis or embolism of mesenteric arteries or veins produce ileus and often gangrene (patients of middle age with cardiovascular disease).

In general the diagnosis of intestinal obstruction is made from the history and examination of the patient. Intermittent pain centering about the umbilicus comes on with a crescendo-decrescendo periodicity and is associated with synchronous intestinal noises heard with a stethoscope. In cases of complete obstruction the constant pain is interrupted by exacerbations of the griping, twisting pain of intestinal colic. Vomiting follows the onset of pain, first with expulsion of gastric contents, later bile, then the stercoraceous material from the intestine. If the obstruction is low in the intestinal tract vomiting may not occur for several days. In the absence of peritonitis, distention of the abdomen occurs without rigidity of the abdominal wall and the temperature is not elevated. If the abdominal wall is thin, tympanitic

gas-filled loops of intestine which are visible and palpable display the contraction waves of hyperperistalsis. Drop-lets from the walls of a distended loop under tension produce a tinkling sound as they fall into the puddle of liquid below. Inability to evacuate the bowels is the rule.

In obstruction of the small intestine the lower intestine may empty. With intussusception, mesenteric thrombosis, and malignant tumors a liquid small bloody mucous stool is common. Within 24 hours after the onset of obstruction an aseptic serous transudate of 500 to 1000 cc of clear amber fluid occurs in the peritoneal cavity. The injected vessels of distended intestine indicate a peritonitis with loss of the normal absorptive power of the peritoneum. The transudate becomes increasingly turbid on the third and fourth day but without perforation of the intestine bacterial cultures may be negative. Examination by roentgenograms show the "ladder" appearance of fluid levels in gas distended loops of small intestine. Gas in quantity is not seen in the normal small intestine after the second year of life. Dehydration from the loss of vital body fluids through vomiting leads to alkalosis if the predominant loss is gastric acid, or acidosis if the predominant loss is alkaline intestinal juices. In untreated cases the blood becomes concentrated as shown by increasing hemoglobin values and a flushed toxic state develops with irritability, fall in blood pressure, rapid pulse, prostration, circulatory collapse, delirium, and death usually from septic peritonitis.

Pathological Physiology — When the normal movement of intestinal content is interrupted there first occurs a

stasis proximal to the obstruction. This increases intraluminal pressure which serves as a stimulus to increase peristalsis and augment the pouring out of intestinal juices. The increased fluid volume and forceful peristalsis in turn add to increased intraenteric pressure. L. Sperling²⁰¹ has shown that through this mechanism absorption from the bowel is decreased early in obstruction. Local circulation in the intestinal wall is impaired by the progressive increase in pressure from within the intestinal lumen. Venous stasis with edematous swelling and infiltration of the intestinal wall with leukocytes then follows. Impaired viability from circulatory deficiency favors permeation of toxic materials and bacteria through the bowel wall. Hemorrhagic infarction results in local necrosis, perforation, and peritonitis.

The general symptoms and toxic state which follows intestinal obstruction are due to interruption of the normal physiologic functions of the intestine resulting in alteration of the blood chemistry. One change in the blood which is always found is a rise in blood urea nitrogen regardless of the level at which obstruction occurs. M. A. Falconer and A. Lyall²⁰² have demonstrated this change and also have shown that a tendency to alkalosis as indicated by a rising CO_2 combining power follows the drop in blood plasma chloride which is proportional to the amount of vomiting in pyloric obstruction.

Experimental evidence is offered by W. d'A. Maycock²⁰³ to show that the supposed toxic action of peritoneal transudate in the presence of nonviable intestine does not account clinically for the circulatory collapse. The loss of whole blood plasma from the circulation is believed by H. G. Scott²⁰⁴ to accompany shock which is the direct cause of death. There is insufficient evidence of

direct absorption of toxic products from a strangulated loop of bowel.

S. Haerem, G. M. Dack and H. Wilson²⁰⁵ present experimental evidence to show that toxins are not absorbed from a closed jejunal loop. However, J. S. Hibbard and A. J. Kremen²⁰⁶ conclude from experiments on dogs that the "volatile bases" in an obstructed loop, which may be increased by the feeding of meat, can cause severe toxic symptoms and death. Importance is attached to the rise in blood potassium in intestinal obstruction by J. Scudder, R. L. Zwemer and A. O. Whipple.²⁰⁷ Hyperpotassemia causes fall in the blood pressure and pulse changes similar to the circulatory condition found in adrenal insufficiency. This is due to the loss of electrolyte and fluid from vomiting and failure in the absorption of intestinal contents. By the parenteral administration of sodium chloride solution a favorable effect on potassium metabolism relieves the symptoms. J. Bottin²⁰⁸ presents experimental evidence to explain the more rapidly fatal condition of a high intestinal obstruction. With obstruction below the pancreatic duct a reflux mechanism from intraduodenal pressure produces a cellular necrosis in the pancreas and may also affect the liver. In animals with a high intestinal obstruction, he showed that life could be prolonged by ligation of the pancreatic duct.

Treatment—Treatment is directed towards the relief of distention by **suction tube drainage** devices or by enterostomy, restoration of body fluids and the acid base balance of the blood, and the removal of the obstruction.

Congenital Defects of the Intestine

Congenital Stenosis of the Pylorus—This occurs most commonly in first born male babies. The cause is rarely a true stenosis but a hyper-

trophic muscular ring at the pylorus which constricts the outlet of the stomach by its spastic contracture. Vomiting occurs as the chief early symptom about the third to sixth week after birth and is forceful and copious because of gastric retention. Waves of hyperperistalsis may be visible as they traverse from left to right across the upper abdomen which is scaphoid. The peristaltic waves stop at the pylorus represented by an olive-shaped mass which may be palpable or visible. Dehydration and weight loss may follow the onset of vomiting with remissions. Medical treatment with antispasmodics, frequent small feedings, alkalies, and thick cereal feedings should not be persisted in if the child does not show improvement in 10 days. The Rammstedt type of pyloroplasty by which the hypertrophic muscular pylorus is divided longitudinally and separated from the mucosa offers the best means of surgical cure. One-half per cent procaine local anesthesia and the use of fine annealed stainless steel wire sutures reduce postoperative complications. The upper right rectus incision should be made low enough to avoid the relatively large, low-lying liver of the baby. The use of catgut sutures should be avoided in closing the abdomen because the unfavorable reaction of the tissues to foreign protein and the coincident delay in healing which favors postoperative disruption of the wound.

Intestinal Atresia—This is rare but occurs most commonly as imperforate anus which may be associated with atresia or congenital absence of the rectum. Failure of the baby to pass meconium may prompt examination which reveals an imperforate anus. Simple incision of the occluding membrane may be all that is needed. T. B. Jones and J. J. Morton²⁰⁹ advises postoperative dilatations of the anus to prevent partial

obstruction from stenosis. For this purpose small glass test tubes in graduated sizes work well when lubricated.

Atresia is rare in the colon but occurs in the ileum at the attachment of the vitello-intestinal duct and in the duodenum usually below the papilla of Vater. Vomiting, abdominal distention, and colic occur soon after the first food is taken. Obstipation following the passage of meconium and increasing tympanites are characteristic findings in lower obstructions. *Early operation* is imperative in these cases. Decompression by suction tube devices or the introduction of an enterostomy tube above the point of obstruction or below it for purpose of feeding are not sufficient. The *division of constricting bands* will relieve obstruction when an intact intestinal lumen is present. Enterostomostomy is required when atresia is found.

An 8-day-old male baby recently observed had been regurgitating all feedings as soon as swallowed since birth. At operation the stomach was found to be greatly distended. A tube introduced into the stomach released a quantity of viscid, amber, acholic liquid, tinged with blood. The marked capillary oozing from all parts of the wound precluded further exploration. Bleeding internally and from the wound could not be controlled by sutures and death supervened in 36 hours, despite administrations of blood transfusions and glucose solution. At autopsy a congenital atresia of the gastric cardia and also of the pylorus was found. Congenital atresias of this type are not uncommonly associated with hemorrhagic disease of the newborn.

Internal Hernias, Hyperfixation, and Intestinal Malrotation—These are less apt to constitute a surgical emergency since the obstruction usually is incomplete. Clinical diagnosis is difficult but roentgenography is helpful. A *short-*

circuiting operation to relieve the obstruction is advised by T. B. Jones and J. J. Morton,²⁰⁹ who also stress the importance of the free use of **parenteral saline, glucose and transfusion**.

It should be remembered that debilitated babies do not tolerate transfusion well and death following such procedure may be attributed to disease when overloading of the circulation by the forceful intravenous injection of citrated blood is actually the cause. The operative procedures for correction of intestinal obstruction in babies is best done with nonabsorbable sutures and ligatures, preferable fine silk for ties and fine (35 and 36 gauge) annealed stainless steel (18-8) wire for closure of the abdomen.

Meckel's Diverticulum—This is a congenital anomaly of the ileum resulting from failure of complete obliteration of the vitellointestinal duct during early intrauterine life. Obstruction of the ileum is produced by invagination of the bowel at the level of the diverticulum through mechanical factors which interfere with normal peristalsis. Colic, vomiting and gaseous distention of the abdomen, scanty liquid stools containing mucus and blood, and the presence of a sausage-shaped mass in the right lower quadrant suggest intussusception. The *diagnosis* of Meckel's diverticulum is seldom made before operation for relief of the intussusception which causes the symptoms of intestinal obstruction. To prevent recurrence of the intussusception the *diverticulum* should be **resected** and the *ileum* **closed**. A technic similar to appendectomy is appropriate in most cases for removal of the diverticulum.

Inflammation, ulceration, and perforation with peritonitis are the most common pathological changes affecting the sac. Islands of ectopic acid bearing cells in the mucosa predispose to perforating peptic ulcer of the diverticulum. Sym-

toms simulate appendicitis. Resection of the diverticulum is indicated.

Dolichocolon—This is a congenital elongation of the colon due to hyperfixation of the upper portion and a long mobile mesenteric attachment of the lower portion of the sigmoid. This condition may exist without producing symptoms but in middle life abdominal complaints suggesting partial obstruction may occur. Aerocoly, borborygmus, and distention are intermittent. Chronic dyspepsia with pain in the ileocecal region may suggest chronic disease of the appendix or at times the symptoms may simulate colitis. Painful abdominal crises described by C. R. Bocca²¹⁰ are characteristic of dolichosigmoid and are relieved by **antispasmodics** and **hot stupes** to the abdomen. The symptoms, however, tend to recur or persist and may be interrupted by an acute condition arising from volvulus, adhesions, pericolicitis, or occlusion of mesenteric vessels.

The *diagnosis* is established by barium enema roentgenograms, which show redundant loops of sigmoid lying in both sides of the abdomen and may reveal the site of obstruction.

Treatment—Surgical treatment is **sigmoidectomy**. The Mikulicz type of resection in stages gives the lowest mortality. Preoperative preparation includes the use of a **nonresidue diet, repeated enemas** and **colonic irrigations**, and in the absence of obstruction a **mild purgative** of castor oil may be used.

Intussusception

Intussusception is the invagination of one part of the intestine into another and is the chief cause of mechanical ileus in children. Over one-half of the cases occur in infancy.

C. Pecchio²¹¹ has classified this condition anatomically as an invagination of (1) ileum into ileum, (2) ileum into

colon, (3) ileum through ileocecal valve into colon, and (4) colon into colon. It occurs chiefly in males. Any defect of the intestinal wall causing a protrusion of mucosa into the lumen with an associated forceful peristalsis favors intussusception. However, these are cases in which no exciting cause is apparent. These may represent instances where hyperperistalsis of an enteritis or prolapse of the ileum through the ileocecal valve have initiated the invagination process. In adults the cause is commonly a benign or malignant tumor of the small or large intestine which is carried downward by peristalsis. Ulceration as in typhoid fever or enlargement of Peyer's patches may less commonly be a cause. Meckel's diverticulum by invagination into the ileum may form the apex of an intussusception. G. Groenberger^{21,2} believes that acute invagination of the intestine is more common in the United States, England and Denmark because of the general misuse of purgatives in these countries.

Diagnosis—Diagnosis of acute intussusception can be made in most cases by physical examination. The infant or young child suffering severe pain during the forceful spasms of the bowel will draw up its legs and cry but is quiet between paroxysms. Vomiting is not as continuous and tympanites is less marked than in the early stages of other types of acute ileus. A pallor and rapid pulse with moist skin and subnormal temperature simulating shock is often seen at the onset. Frequent small mucous stools streaked with blood are expelled with much straining. A mass may be felt in the ileocecal region. If the intussusception progresses to the hepatic flexure it disappears due to the overlying liver but becomes palpable when the left colon is involved. Rectal examination should always be done, for in a large majority

of patients the mass is palpable through the interior rectal wall. X-ray examination by barium enema is helpful and often shows the typical notched appearance where the barium is stopped by the apex of the intussusception. The barium mixture does not readily flow through the ileocecal valve in a retrograde direction so that obstruction in the ileum may not be localized from the films when the colon is not involved by the invagination process.

Treatment—Treatment is directed first towards reduction by *manipulation* if the condition is diagnosed in the first 12 hours. With the child suspended upside down by the legs a jolting compression of the abdomen by hanging the child over one's shoulder may result in reduction of the mass. Pressure applied at the apex or distal end of the mass is difficult to obtain through the abdominal wall. This is more easily done by hydrostatic pressure from the injection of fluid into the rectum. *Normal saline* or *barium sulfate mixture* may be used. The enema reservoir should not be elevated more than 3 feet above the level of the anus. By compression over the left iliac fossa, return flow of the solution may be retarded while careful manipulation of the apex of the mass begins reduction. As the mass recedes more solution is introduced to maintain the intraenteric pressure. G. Groenberger states that 50 per cent of the acute cases can be successfully reduced by conservative measures within 12 hours after onset, but that in babies reduction by manipulation is not probable after this time interval.

If a fair trial of conservative measures is ineffectual, *operation* should not be delayed. At operation manual reduction of the mass is obtained by squeezing the distal end. The proximal end should never be pulled. If gangrene of a bowel

segment is found, **resection** with an end-to-end or end-to-side anastomosis results in a high mortality. A simple proximal enterostomy using a small rubber tube is better. A stage operation may be used in older patients, but infants do not tolerate abdominal colostomy well. Recurrence of the intussusception is prevented by removal of tumor or other cause of the invagination. Invagination which occurs during the throes of a death agony or post mortem involves the small intestine in 2 or more areas and is recognized at autopsy by the absence of adhesions between the intussusceptum and intussusciens and the lack of edema and injection of vessels.

Volvulus

The occurrence of kinks or angulation of the intestine forms a small proportion of acute bowel obstructions. It is most common in the left colon of middle-aged men. Predisposing factors include dolichosigmoid, a diet containing excessive amounts of cellulose foods, strong purgation and peritoneal adhesions from a previous abdominal operation. The symptoms are those of acute obstruction of the colon. Severe colic and marked gaseous distention of the intestine occur early with inability to move the bowels. Barium enema may localize the point of obstruction but the exciting cause may not be apparent.

Treatment—Treatment is **operation without delay** since the twisting of the bowel through an arc of 180 degrees or more which causes the obstruction also produces coincident obstruction of circulation. This favors early gangrene and perforation with peritonitis and leaves less time for procrastination or scientific tests and studies. The loop of bowel is untwisted and examined for viability of the damaged loop. A nonviable segment is resected by the Mikulicz stage opera-

tion. Drainage of the peritoneum is best established through the use of a glass tube drain anchored to the skin and the wound closed around it. If there is infected material, especially bloody fluid in the pelvis, another glass tube drain should be inserted through a stab wound in the perineum between the coccyx and rectum to drain the pelvic peritoneum. Other drains are less effective where free escape of septic fluid from the peritoneum is required over a period of several days. The use of interrupted sutures of annealed stainless steel wire for closure of the abdominal wall in layers gives the best prospect of healing *per primam* in septic cases. A possible pyoderma in which a necrotizing infection spreads between the fascia and aponeurosis layers in some of these cases may prove fatal unless early recognition with free opening of the wound and further incision as required for drainage is done promptly.

Adhesions

Bands of fibrous tissue or fixation of intestinal surfaces following previous peritonitis are common causes of intestinal obstruction. The past history often reveals an acute abdominal condition (diverticulitis, appendicitis, typhoid or other severe enteritis) or operation for a septic condition which required drainage. A distorted abdominal scar suggests previous operative drainage when the history is uncertain, and suggests the presence of peritoneal adhesions.

The *symptoms* are those of an acute ileus which may involve either the small or large intestine.

Treatment—**Operation** soon after the onset of the signs of obstruction gives the best chance for recovery for the mortality is greatly increased if operation is delayed until gangrene of the intestines or peritonitis from perforation supervene. In early cases separation of

adhesions may be all that is required. **Later resection of nonviable bowel** and **drainage** are required as conditions demand.

Chronic Inflammatory Diseases of the Intestine

Chronic disease of the intestinal wall produces symptoms of chronic intestinal obstruction by stenosis from edema, ulceration, and cicatricial changes.

Intestinal Tuberculosis—This is found secondary to pulmonary tuberculosis, usually in males before the age of 40, and is twice as common in negroes as in whites. Ingestion of sputum bearing acid-fast bacilli escape the germicidal effects of digestive juices and attack the lower ileum and cecum. Chronic dyspepsia, vomiting, and anorexia with progressive debility and weight loss are often accompanied by alternating constipation and diarrhea. A painless sausage-like mass may be palpable in the right lower quadrant. Death is due to the progressive pulmonary lesion in most fatal cases. **Resection** and **ileocolostomy** should be considered for relief of obstruction if resolution of the process is not obtained from medical treatment and if the patient shows evidence of resistance to the disease by a localized hyperplastic form of reaction in the intestine.

Nonspecific Intestinal Granuloma—This has been established as a pathologic entity since 1932. A comprehensive review of the literature is given by M. Lick.²¹³ Various names have been applied to this condition (regional ileitis, terminal ileitis, benign granuloma of the intestine, infective granuloma, Crohn's disease, etc.). The cause is not known but thought to be low grade infection, probably a streptococcus, which first produces a chronic lymphedema of a segment of intestine and its mesentery. This is followed by

ulceration of the mucosa along the mesenteric attachment. The affected segment is heavy, thickened, purplish-red, and is adherent to other loops of intestine. There is a plastic exudate on the peritoneal surface, and the mesentery which holds large lymph nodes containing giant cells is thick and stiff.

The disease is not common but is found chiefly in young adult males in which the onset is usually acute with signs and symptoms simulating appendicitis. It is not unusual to find that chronic cases have undergone appendectomy without relief of abdominal symptoms. Recurrent pain across the lower abdomen with intermittent diarrhea, fever, progressive weight loss, anemia and weakness are persistent symptoms. Backache and vague pains in the legs may be troublesome. The small frequent loose stools at times show blood and mucus. As the condition progresses a chronic obstruction results from stenosis of the diseased portion of intestine. A curved cylindrical mass is often palpable in the right lower quadrant since the terminal portion of the ileum is frequently involved. Gastrointestinal roentgenograms aid in making the diagnosis. The "string sign" of an irregular constricted lumen in one or more segments of the ileum is typical but not pathognomonic. The ultimate formation of abscesses and fistulae are seen in the late cases.

Treatment—Medical treatment is of no benefit though spontaneous cure is thought to occur in a few cases. A **bland, nonresidue diet** should be given. **Short circuiting operations** to relieve the obstruction give relief in about one-half of the cases in which it is employed. The treatment of choice is **early excision** of the granulomatous segments and **end-to-end anastomosis** with **glass tube drainage** of the peritoneum. **Ileo-cecectomy** and **ileocolostomy** are

adaptable to many cases. To prevent "recurrence" of the disease all granulomatous areas should be removed. There may be "skip areas" of apparently normal intestine between segments showing granulomatous change so that removal of 4 to 5 feet of small intestine may be required to eradicate all of the diseased areas.

Malignant Lymphogranulomatosis (Hodgkin's disease)—This is rarely the cause of intestinal obstruction. The *etiology* is unknown. L. Efskind²¹⁴ presents evidence to show that the *pathogenesis* is a virus which produces a primary ulceration of the mucosa followed by involvement of the regional lymph nodes. The intestinal type produces stenosis of the bowel from ulceration and pressure from the massive enlargement of mesenteric lymphatic structures. Diarrhea-like steatorrhea is accompanied by the symptoms of an increasing intestinal obstruction and may be associated with an intractable generalized pruritus and an abdominal mass. *Diagnosis* is made by biopsy. *Treatment* is **resection of the involved intestine** to relieve obstruction and **roentgen ray therapy** in small doses over a long period to retard the advance of the disease

Tumors of the Intestine

Most tumors of the intestine are malignant and involve the colon. Tumors of the small intestine are rare and are seldom diagnosed unless they become large enough to produce the symptoms of obstruction. Argentifine tumors arise from the crypts of Lieberkuhn and may produce intussusception. T. E. Wyatt²¹⁵ reviews the subject and states that of 159 reported cases, 36 showed metastasis, but with resection the prognosis is good. Sarcoma of the small intestine is rare and is irradicable by resection in relatively

small percentage of cases. Polypoid adenomata and lipomata are uncommon but may produce obstruction requiring enterectomy.

Benign Adenomata of the Colon (Polyposis Coli)—These are common and may exist without causing symptoms. Syndrome suggesting colitis with blood and mucus in the stools and obstruction from intussusception of the colon may occur, requiring partial colectomy. The **stage operation** after the Mikulicz plan of resection is desirable. The greatest danger from adenomata of the colon is the development of carcinomatous change which occurs in over one-third of the cases.

Carcinoma of the Cecum and Ascending Colon—Cancer of the colon is typically adenocarcinoma, of which group the medullary variety is most common. Nineteen per cent occur in the cecum, according to J. Fraser²¹⁶ in his review of 900 cases of carcinoma of the colon. Growths in the cecum often advance until obstruction from massive tumor or weakness from anemia prompt the patient to seek medical aid. Severe secondary anemia frequently accompanies carcinoma of the cecum or ascending colon. Similar lesions in the left colon are found in patients who commonly have a ruddy complexion and the general appearance of good health. The anemia responds poorly to liver and iron medication and may require repeated transfusion to bring hemoglobin values within favorable range. Some investigators have felt that anemia in these cases is the result of chronic small hemorrhages over a long period, yet the amount of blood passed by stool does not confirm this view as a rule. Since 80 per cent of fluids are absorbed through the right half of the colon it is conceivable that putrefaction products of a large fungating mass together with excessive bacterial products in this region

enter the general circulation by absorption resulting in a constant state of toxemia which causes the marked depletion in red blood cells and hemoglobin. Massive hemorrhage from the carcinoma is rare. Progressive weight loss and diar-

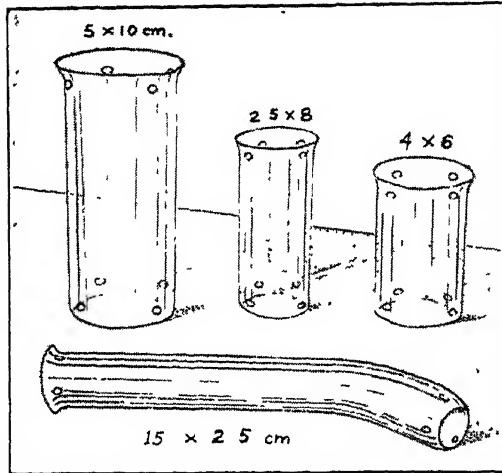


Fig 1—Glass tube drains, which are advocated for prolonged drainage of the peritoneum have been found more adequate than other types commonly used. Perforations near the ends facilitate anchoring the tube with sutures. (Surgical Clinics of North America, Dec., 1938. Clinic of Dr. W. Wayne Babcock.)

rrhea followed by anemia and the signs of obstruction are associated with a mass which may be felt in the right iliac fossa. Perforation and local peritonitis with abscess formation occurs with advanced growths and increases the dangers of resection. The early signs of change in bowel habit may be overlooked or neglected by the patient. Fetid loose stools containing dark blood and mucus suggest a large fungating mass.

Carcinoma of the Transverse Colon—This produces less weakness and anemia. The early change in bowel habit is significant but is usually neglected by the patient. Intermittent diarrhea with mucus, melena, and a gradual progressive constipation precede frank symptoms of obstruction which is always a late sign.

Pain is a significant early symptom in the disease. A hard mass may be palpable when the patient first consults a physician. Complaints which suggest a low-grade obstruction in a patient over 40 years of age should be looked upon with suspicion. Recurrent colic after meals may be the first symptom. Mortality from operation is considerably increased after complete obstruction has occurred.

Carcinoma of the Descending, Sigmoid and Pelvic Colon—This is more often of the scirrhus type and may be difficult to feel through the abdominal wall since the tumor is small and produces obstruction by constriction of the intestinal lumen. Morning diarrhea with tenesmus is highly suggestive of a fungating carcinoma of the rectum. Only growths adjacent to the anus produce pencil stools. The general health is often

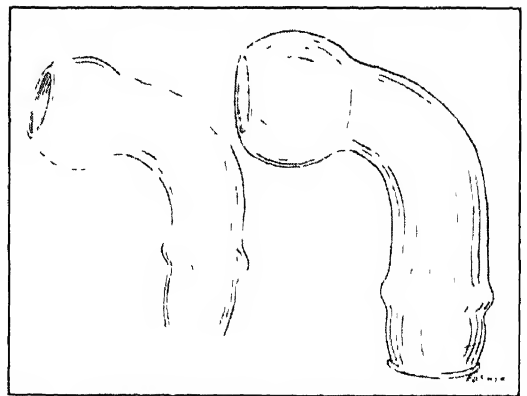


Fig 2—Babcock modification of the Paul tubes. These are glass and are tied in the ends of the colon following the Mikulicz type of resection. Danger of necrosis from tube pressure is avoided by placing the tubes so that they remain outside the abdomen. (Courtesy of Dr. W. Wayne Babcock.)

not visibly impaired until the disease is far advanced. Many patients first consult the physician for the treatment of "hemorrhoids" and the true condition may go unrecognized for weeks or months unless digital examination of the

rectum or endoscopic visualization of the pelvic colon is done before treatment is prescribed.

Treatment—By the nature of the disease, the treatment of colonic malignancy is necessarily *surgical*. With con-

section. Removal of the primary growth relieves obstruction and the patient often shows a remarkable return of strength, vitality and weight gain even in the presence of metastatic nodules in the liver as observed in one patient who is active, in

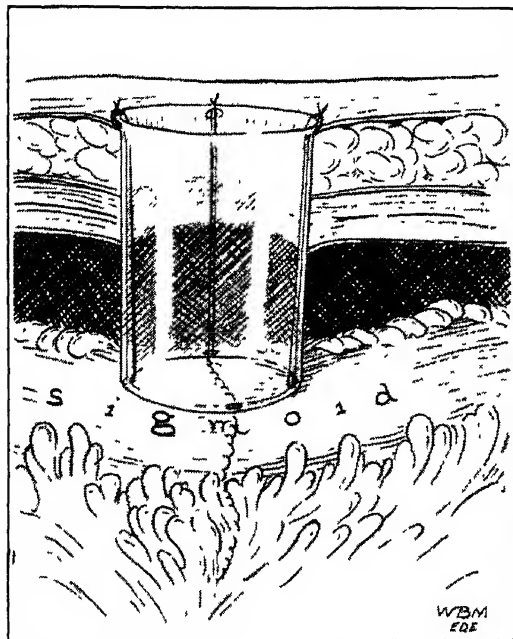


Fig 3—Glass tube drain anchored to sigmoid over line of anastomosis may be a lifesaving measure should a leak develop. The tube may be removed on the second to fourth day after operation, providing there is no evidence of puriform or other drainage (Courtesy of Dr W Wayne Babcock)

stant improvements in technic and management of this condition the operability rate has increased. H Finsterer²⁵ who has had wide experience finds 79 per cent of the cases operable while Sir J Fraser²¹⁶ in a review of 900 cases concludes that 55 per cent to 60 per cent are inoperable when they come to the surgeon. In this country, as elsewhere, the operability rate varies with the individual surgeon, and in some hands is as high as 80 per cent (Babcock). Metastasis to the liver is best determined at the time of operation and necessarily gives a bad prognosis but does not contraindicate re-

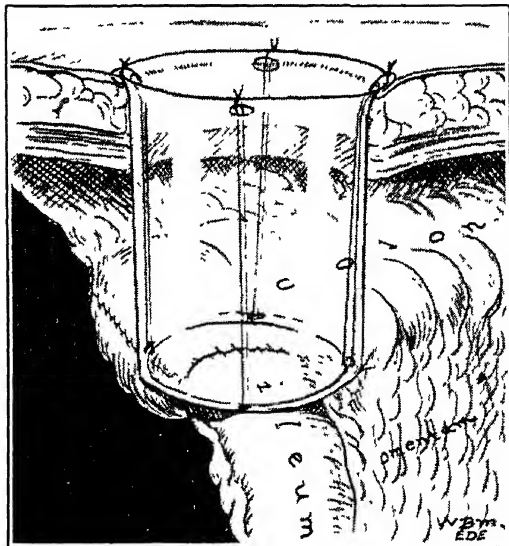


Fig 4—Glass tube drain anchored over line of anastomosis following ileocectomy. The general peritoneal cavity as well as the region of the anastomosis is drained in this manner (Courtesy of Dr W. Wayne Babcock)

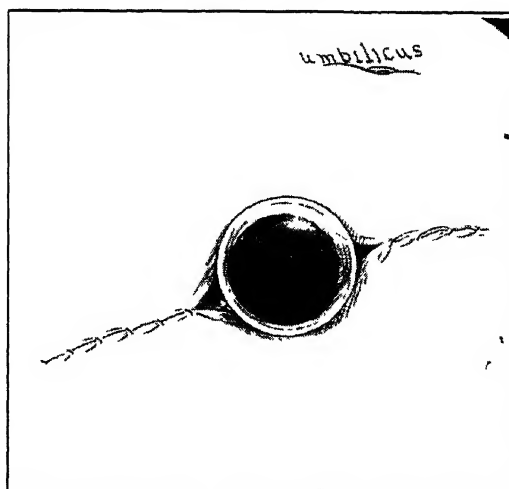


Fig 5—Transverse lower right quadrant muscle-splitting incision 2 days following ileocectomy showing drain guarding anastomosis of the ileocolostomy (Courtesy of Dr W Wayne Babcock)

good nutritional status, and without symptoms 3½ years after resection of the rectum and sigmoid, though typical metastatic nodules were present in the right lobe of the liver at the time of operation.

In certain instances the removal of the primary growth seems to have a retard-

early metastasis, especially in the mesenteric lymph nodes. Drainage of the peritoneum is of first importance because of the possibility of contamination from the intestine in resections and the presence of blood in the peritoneal cavity after closure of the abdomen. Gauze and

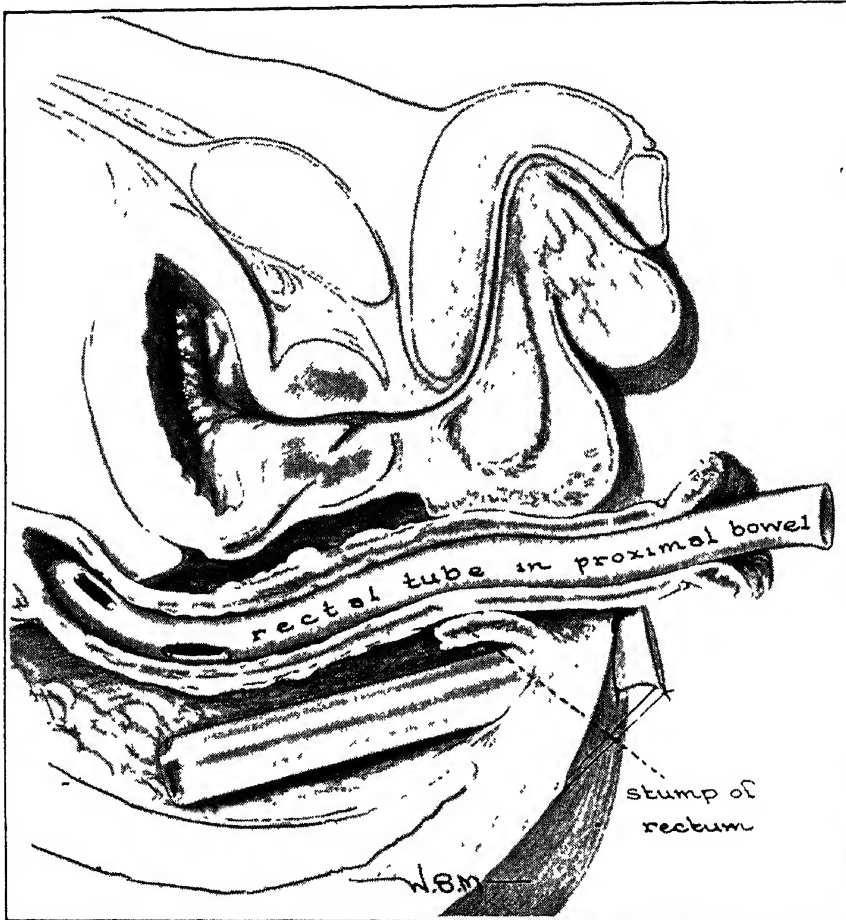


Fig. 6—Following proctosigmoidectomy for carcinoma the pelvis is drained through the perineum by the long glass tube which has multiple perforations near the end. 500 to 1000 cc of serosanguinous fluid often escapes during the first 24 hours after operation. (Courtesy of Dr. W. Wayne Babcock.)

ing effect on distant metastasis. Lesions in the pelvic colon metastasize upward through the lymphatics earlier in the disease than is apparent from gross appearances. It is therefore important in these cases to resect normal bowel and attached mesentery proximal to the growth for these often bear the nidi of

other drains are often inadequate. Retained bloody fluid in the peritoneal cavity furnishes a lush pabulum for virulent organisms (especially streptococci and *B. Welchii*) which may produce a rapidly fatal peritonitis. Specially shaped glass tubes provide the best means for prolonged free drainage of the peritoneum

as shown by W. Wayne Babcock (Fig. 1). By using a tube with flattened end or by anchoring the end of a circular tube to the bowel to guard an anastomosis, herniation of an intestinal loop into the lumen of the tube is prevented.

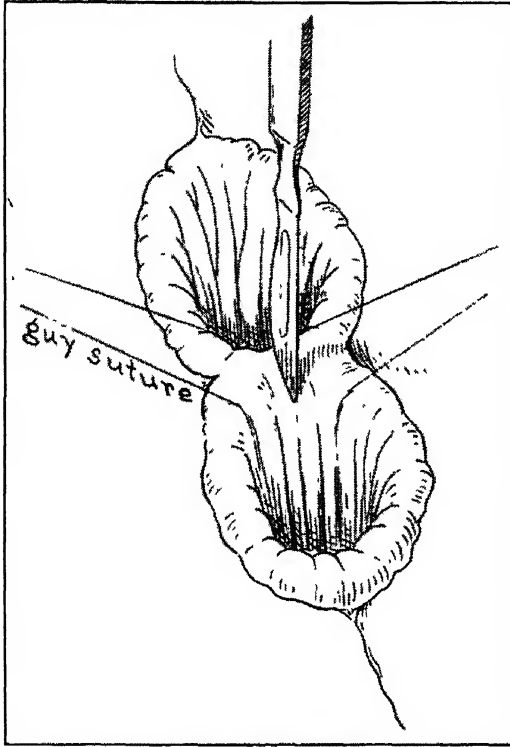


Fig 7—Babcock method of beginning the closure of double-barreled colostomy following resection. A right angle clamp is not used, the spur is divided and sutured with interrupted stainless steel wire (Courtesy of Dr W. Wayne Babcock)

X-ray studies are a valuable aid to early diagnosis and confirm the clinical findings in late cases. Barium should not be given by mouth as it may convert a partial obstruction into a complete obstruction. After barium enema the colon should be emptied by colonic irrigations or by giving castor oil by mouth if acute obstruction is not impending. The filling defect shows destruction of the mucosal pattern which aids in differentiating the inflammatory mass of diverticulitis of the left colon from malignant tumors of this

region. X-ray examinations are not required in carcinoma of the rectum and may be misleading. Rectal growths can be diagnosed by the examining finger or proctoscope. Biopsy is rarely necessary if the growth can be felt because of its typical character.

Preoperative preparation reduces the surgical mortality. The diet should be limited to *soluble foods* which leave a minimum of residue in the colon after digestion. *Repeated enemas* and *colonic irrigations* and the judicious use of *mild purgatives* are employed to empty the intestinal tract as completely as possible. In the presence of *obstruction*, *decompression* preferably by *enterostomy* or *colostomy* is necessary. Since the tumor invades the intestinal wall, *perforation* occurs as a late com-

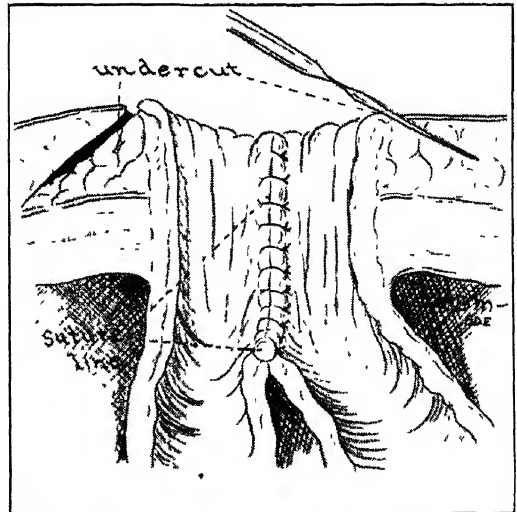


Fig 8—The Babcock closure of colostomy showing spur divided. The skin is undercut to permit the bowel to be returned to the abdomen. (Courtesy of Dr W Wayne Babcock)

plication and requires *drainage* of the abscess. With fungating tumors of the cecum and ascending colon the secondary anemia which is often severe should be relieved by the use of hematinics, liver preparations, and in some cases repeated

transfusions. The use of vaccine preparations either by hypodermic or intraperitoneal injection have found favor with some operators.

The choice of operation depends upon the site of the lesion, the surgical facil-

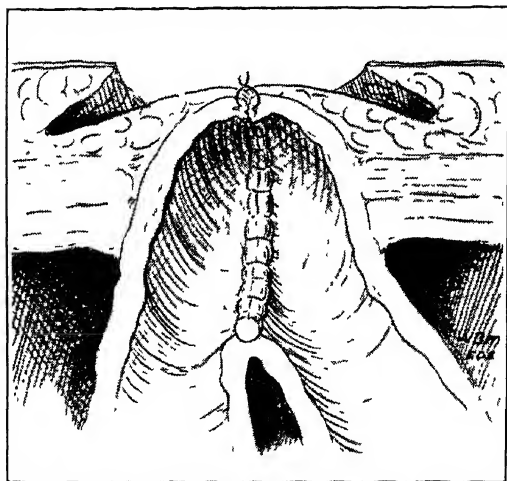


Fig 9—Babcock closure of colostomy. The spm has been divided and the edges of the bowel are united. The skin is not sutured because of the danger of a spreading pyoderma from this infected field. The peritoneum has not been opened. (Courtesy of Dr. W. Wayne Babcock.)

ities available, the complications present, and the general condition and life expectancy of the patient. Resection of the primary growth should be possible in a high percentage of cases. Less radical measures are reserved for patients of advanced age or those with local or general complications which prohibit extirpation of the growth. For lesions of the right colon a 1-stage resection and ileocolostomy with glass tube drainage of the peritoneum is employed. For tumors of the transverse, descending and sigmoid colon a stage operation of the Mikulicz type has given a lower mortality. Tumors of the pelvic colon not amenable to exteriorization for the Mikulicz method of treatment are best resected by a 1-stage abdominoperineal proctosigmoidectomy with formation of a perineal

anus and glass tube drainage of the pelvis. Abdominal colostomy after resection of the rectum and sigmoid is a great inconvenience to the patient because of conventional clothing and psychologic factors which often limits social adjustment after recovery. In skilled hands formation of the perineal colostomy does not add an undue risk from operation and gives much more satisfaction to the patient even when the sphincters cannot be preserved and voluntary control is not obtainable.

Intubation of the Small Intestine

Nonsurgical treatment of intestinal obstruction has received attention recently

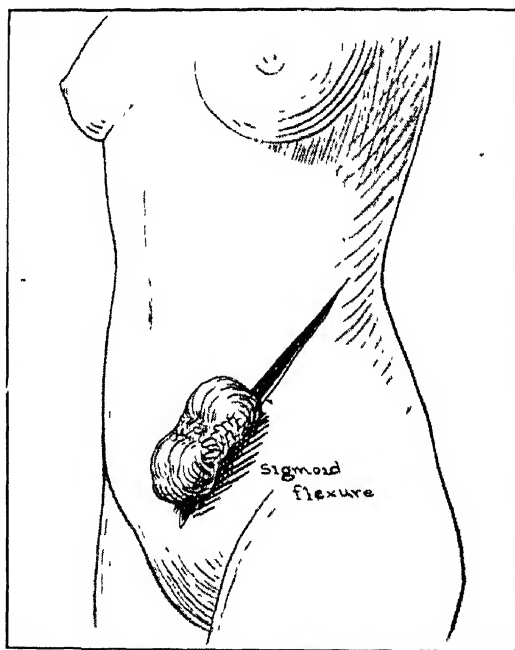


Fig 10—Babcock incision for exteriorizing various portions of the sigmoid. It is a left oblique muscle-splitting incision and gives a strong abdominal wall after closure. (Courtesy of Dr. W. Wayne Babcock.)

through the work of Miller and Abbott, who have devised a special double lumen tube for suction drainage of the small intestine. Normal intestinal action is restored, says W. O. Abbott and C. G. Johnston,²¹⁷ and obstruction from kink-

ing adhesions often relieved when the small intestine is emptied. To accomplish decompression a special rubber tube bearing an inflatable rubber balloon of 50 cc capacity near the end is introduced into the stomach much the same as a Levin or Lyons tube. One lumen of the tube is connected with the balloon and the other has perforations through which intestinal contents may be aspirated in front of the balloon. The passage of the end of the tube through the stomach may require 10 to 12 hours, after which the balloon is inflated with 30 cc of air and progress through the small intestine is made at the rate of 0.5 cm per minute. As gas and liquid are aspirated by constant suction the intestine contracts and forces the balloon forward; 8 to 10 feet of tubing are required to reach the ileocecal valve. The progress of the tube is followed by fluoroscopy and dilute suspensions of barium sulfate injected through the tube may be used to visualize various parts of the small intestine. This procedure is of no value in obstructions of the large intestine. It is time consuming, requires constant attention and the services of a radiologist. The most hazardous element is the possibility of delaying surgical intervention in the presence of strangulation of the intestine or peritonitis. Even with viable intestine the procedure may be particularly trying

to an acutely ill patient who becomes a poorer surgical risk if the nonsurgical treatment is unsuccessful. Successful decompression of the small intestine which does not relieve the obstruction may exhaust an ill patient by prolonged manipulations with the tube. If decompression can be obtained with facility and without taxing the patient's strength too severely the mortality from operation is reduced.

Obstruction Resulting from Roentgen Ray Therapy

Injuries to the intestine were found in 87 per cent of patients by J. A. Corscaden, H. H. Kasabach and M. Lenz²¹⁸ following roentgen-ray treatment for carcinoma of the uterine cervix. The pathological changes seen at necropsy and operation varied from proctitis with inflammation and ulceration to cicatricial stenosis and perforation. These effects were prevented by reduction of dose and size of field. I. A. B. Cathie²¹⁹ reports 2 deaths resulting from intestinal injury in patients treated by x-ray for carcinoma of the cervix. If diarrhea develops during roentgen-ray treatment one should proceed with considerable caution as there is apparently a subnormal tolerance to the rays in some patients. Fibrotic changes in the intestine may produce obstruction as late as 3 to 7 years after the irradiation.

SPLEEN

By FRANCIS L. ZABOROWSKI, M.D.

Acute Abscess of the Spleen

Etiology—Splenic abscess has been reported to occur as a sequel of a great variety of infectious conditions, such as furunculosis, otitis media, erysipelas, staphylococcal osteoperiostitis, osteomyelitis, purulent salpingitis, appendicitis,

gonorrhea, intestinal amebiasis, ulcerative endocarditis, pneumonia, typhoid and paratyphoid fever, puerperal infections, diphtheria, malaria, smallpox and bubonic plague. Splenic abscess may be secondary to a splenic infarct, trauma, splenic torsion, and ectopy. The causa-

tive organisms are usually the staphylococcus, streptococcus, pneumococcus, bacillus coli and ameba histolytica

Signs and Symptoms—The disease may begin suddenly or the onset may be insidious. There is pain and tenderness in the left hypochondriac region with splenomegaly accompanied by chills and fever. The condition is most commonly confused with malaria, from which it is differentiated by the negative blood smears. E. Caldarera²²⁰ reports a case and also reports the results obtained from an experimental study performed with rabbits. In 1 group of animals he traumatized the spleen, in another group of animals he produced an anemic infarct of the spleen by ligating the terminal branch of the splenic artery. Then all the animals were inoculated intravenously with a broth culture of staphylococcus aureus. They all died within from 2 to 7 days. The resulting lesions are different, in a traumatized spleen there appears within the injured zone an aggregation of small abscesses which gradually enlarges and becomes confluent. In the infarcted spleens, however, the inflammatory process begins around the infarcted area, and the latter becomes gradually infiltrated and undergoes purulent changes. The *prognosis* of untreated cases is grave. *Treatment* is always surgical

Splenomegaly

Roentgen Diagnosis of Esophageal Varices—According to G. Lenarduzzi and G. Chiorazzo,²²¹ the presence of varices in the lower segment of the esophagus in roentgenograms taken in the course of autochthonous splenomegaly without hepatic complications shows that splenomegaly is of the fibrous congestive type. In this type of splenomegaly there is a primary disorder of the splenic circulation with consequent stasis of the

blood in the spleen, which is followed by the establishment of a collateral circulation, early in the course of which the esophageal varices appear.

Ulcer and Gastroduodenitis in Splenomegaly—According to E. Greppi and A. Forconi,²²² gastric, duodenal and gastroduodenal inflammation and passive congestion associated with similar conditions of the spleen and the liver show an early phase of gastric, duodenal or gastroduodenal ulcer. The clinical symptoms vary from mild to grave digestive disturbances. In certain cases there is either gastralgia or the complete syndrome of gastric or gastroduodenal ulcer. In all cases the chemistry of the gastric secretion is altered and there is a tendency to the production of local hemorrhages. Roentgen examination of the gastrointestinal tract shows the various evolutionary phases of gastric or gastroduodenal ulcer from simple duodenitis to typical ulcer. The authors report 9 such cases. Roentgen examination of the gastrointestinal tract showed simple or erosive duodenitis in 7 cases, phlogosis of the stomach and cardias with perivisceritis in 1 case and a chronic ulcer of the lesser curvature of the stomach with perivisceritis in another. In all cases the clinical symptoms corresponded to the evolutionary phase of the ulcer. In 1 case the repeated examination of the gastrointestinal tract showed simple duodenitis, which evolved to erosive duodenitis with formation of punctiform niches in 4 months. In another case, roentgen examination showed the regressive evolution of a small juxta pyloric ulcer to diffuse gastroduodenitis in the course of 4 months of medical treatment. The authors believe that inflammation and passive congestion of the spleen alone or in association with similar conditions of the liver are due to local disturbances of the preportal circulation. The condition re-

sults in the establishment of a special form of diffusing and progressive inflammation and local passive hyperemia, which induces the development and evolution of gastric, duodenal or gastroduodenal ulcers.

Treatment—The *treatment* consists in *splenectomy* or *ligation of the splenic artery*, which is advisable as soon as possible after establishment of the roentgen diagnosis owing to the fact that the patient is menaced by the production of intense hemorrhages of varicose origin or by complications of the liver. The operation in certain instances is followed by the disappearance of the esophageal varices from the recently taken roentgenograms. When thrombosis of the gastric coronary vein exists, the varices are not modified. Even in these cases splenectomy is of value, as it prevents further disturbances of the portal circulation, the hemorrhagic diathesis and the cirrhotogenic influence of the congested spleen on the liver. According to the author the esophageal varices are the result of the association of stasis of the splenic blood with that of the liver and of the various territories of the stomach. It is still unknown why in certain cases a gastroesophageal stasis prevails whereas in other cases there are functional disorders and inflammation of the pyloric and duodenal segments with formation of local ulcers.

Epinephrine in Malarial Splenomegaly—*Ascoli's treatment* for malaria consists in intravenous injections of progressively increasing doses of *epinephrine*, which are administered daily until 30 injections have been given. S. Livierato²²³ treated 7 adults presenting malaria of the daily, tertian and irregular types of from 2 to 14 years' duration. There was intense splenomegaly and anemia in all cases and the patients were in poor general condition. Treat-

ment was discontinued by 2 of the patients. Treatment gave satisfactory results in the other 5 cases. The author thinks that the treatment is harmless. In some cases there is a transient intolerance but treatment can be continued without interruption. While the treatment is being taken the appetite and general condition of the patients improve, weight increases, the malarial skin tinge disappears, the blood improves and splenomegaly is progressively reduced. In the group of patients observed by the author at the end of the treatment the weight of the patients increased from 4 to 9 kg., erythrocytes increased from 1,000,000 before treatment to 2,500,000 per cm. of blood after treatment. Hemoglobin increased from 20 to 40 per cent. The results of the treatment are permanent.

Splenectomy—The splenomegalies which do not require operation include the splenic hypertrophies of a tumoral nature, such as Gaucher's disease, Hodgkin's disease and leukemia. Aside from the splenectomies in which surgical treatment is dangerous or at least useless, there is another category in which surgery is not necessary. With this group, the author classes all those cases in which medical treatment suffices to effect cure or improvement, for instance, the splenic changes of syphilis, leishmaniasis, bilharziasis and malaria. On the other hand, in the presence of 1 of these splenomegalies of known cause in which the medical treatment is of little influence, recourse to splenectomy may be necessary because of disorders in the blood, the vessels or the liver. Increase in size of the spleen, progressive anemia and hemorrhages are the chief indications for surgery. Before an operation is decided on it is important to determine the functional capacity of the liver. An irregular and hard liver with sharp outlines in a person with poor general condition

must be regarded as a contraindication to the operation. The author refuses to perform an operation in cases in which the urea content of the blood is below a certain level. After the liver has been thoroughly examined for contraindications to surgical treatment, the vascular system should receive attention. Thrombosis of the portal vein and adhesions between the spleen and the walls of its bed are contraindications to splenectomy. Discussing 115 splenectomies R. Grégoire²²⁴ says that in the first 15 operations he had an immediate mortality of 33 per cent. In the later cases the mortality fell to 7 per cent. As regards the late results of splenectomy for splenomegaly, he says that the hemorrhagic tendency is nearly the only danger that has to be feared. Of 37 patients who were operated on, 9 did not present hemorrhage, while the 28 others had had hemorrhages before the operation, such as epistaxis and bleeding from the gums. Of the aforementioned 9 patients, 2 had malarial hypertrophy, 2 had tumoral hypertrophy, 1 had kala-azar, 1 had leukemia and 3 had splenomegaly of unknown origin. The 28 splenomegalies with considerable hemorrhages were for the most part of the type characterized by the presence of Gamma nodules. Of these 28 patients, 21 remained free from hemorrhages, but the 7 others had recurrences of hemorrhages. The late results of splenectomy are good, for the author observed 81 per cent of permanent cures. They were entirely free from those changes in the blood and in the capillaries which make the prognosis unfavorable.

E. L. Eliason and J. Johnson²²⁵ report on a series of 53 splenectomies. There were 21 cases of splenic anemia (Banti's disease). Among these, there were 8 deaths, all occurring in patients with advanced disease. On the basis of

this experience, the authors believe that operation is justified in the late stage only when the size of the spleen causes great discomfort. Of the 13 surviving patients, all but 1 are either well or their condition is improved. There were 12 cases of hemolytic icterus. There was no operative mortality and all but 1 of the patients are well. It is preferable in this disease to perform splenectomy during a remission, but occasionally operation is necessary during an acute exacerbation. Seven patients presented purpura hemorrhagica. There were no operative deaths. Operation should be performed both in the acute and chronic cases, if bleeding does not respond promptly to conservative measures. There were 5 patients with rupture of the spleen, all of whom recovered from the operation and are well after from 1 to 11 years' follow-up. Splenectomy was performed on 2 patients suffering from subacute bacterial endocarditis with splenomegaly. One died and the other was not followed up. Riesman and his co-workers believe that splenectomy for this condition prolongs life and renders the patient more comfortable. Multiple lymphogenous cysts were diagnosed in 2 patients. Both recovered and are well following operation. Splenectomy was performed in 1 case of syphilis associated with splenomegaly. The patient, prior to operation, failed to respond to antiluetic therapy, but thereafter responded well. Operation was performed in 1 case of primary splenic tuberculosis with an excellent result. It also was performed in 1 case of myelogenous leukemia, this patient died 3 months after operation. In 1 case of aplastic anemia associated with purpura, splenectomy was performed as a last resort. The patient died on the eighth postoperative day.

Indications for Splenectomy in Childhood—L. K. Diamond²²⁶ emphasizes the greater severity of congenital hemolytic anemia in childhood, and on the need for early operative treatment to prevent fatal termination. The results of splenectomy in this disease were most gratifying. Particularly striking were the growth and development which were found to be retarded during the period of observation before operation. Platelet crises with intravascular thromboses may occur after splenectomy and cause serious symptoms. Eight children with splenic anemia or leukopenic splenomegaly were operated on. In these cases the diagnosis was established by the exclusion of infections and by the finding of a moderate hypochromic anemia, a constant leukopenia, and a thrombocytopenia. In general the results of operative treatment in this group were fairly good, although not so satisfactory as in congenital hemolytic anemia. Sixteen cases of splenomegaly with early gastric hemorrhage were studied. In 11 of these, splenectomy was performed. The results were questionable, since hemorrhage tended to recur even after operation. As the probable lesion in such cases is thought to be an obstruction in the portal or splenic veins, removal of the spleen alone can hardly be expected to benefit all children with this disturbance. The additional procedure of tying the coronary vessels and performing an anastomosis between the omentum and peritoneum has seemed to result in less frequent hemorrhages. In the study of a group of 28 cases with idiopathic thrombocytopenic purpura hemorrhagica, it was thought advisable to perform splenectomy in 8 cases. This was done to prevent fatal or serious recurrent hemorrhage, after the usual medical therapeutic agents had failed. In this group the operation gave

moderate relief of the symptoms in 2 cases, and apparent complete relief in 6. Five children with Gaucher's splenomegaly were treated by splenectomy. The indications for operation in this disease were: increasing fatigue and limitation of activity caused by the enlarging spleen, the development of hypochromic anemia with leukopenia and thrombocytopenia, and retardation of the growth and development of the child. In this group the operation produced immediate relief from these troublesome symptoms. Although it still may be too early for a final appraisal of the state of the disease in each of these children, no extension to the skeletal system has been noted following splenectomy.

MESENTERY

Influence of the Mesentery in the Production of the Radiological Aspects of Intussusceptions—On the basis of numerous radiological examinations of intussusceptions in different segments of the digestive tube, B. Bonomin²²⁷ is convinced that the mesentery is not limited as usually described in the radiological picture, a simple arc with walls more or less folded. This is only the shortest form of a more complex curve, sinusoid or ellipsoid, in which the mesentery has the function of an axis. The radiological expression of the sinusoidal or ellipsoid course is a polycyclic contour of the intussusceptum with arches in alternate directions, its folds appearing as fans pointing in opposite directions. The geometrical and anatomical characteristics of the mesentery influence the characteristics of the intussusception in the following manner: the root of the mesentery prevents the accumulation of any considerable number of loops in the intussusception when the mesentery is elongated. On the other

hand, the forms of intussusception in which most of the small intestine is invaginated are favored by a short or peduncular type of abdominal insertion. The nearer the entrance of the intussusceptum to the root of the mesentery, the longer is the invagination. The longer the intestinal insertion of the mesentery is found to be, the greater is the number of loops which can be invaginated. The breadth of the mesentery, the distance between its abdominal and intestinal insertions, is the factor which determines definitively the absolute length of the intussusceptum. The intussusceptum cannot be much greater than the breadth, even when the possibility of elongation by caudal and lateral rotation of the distal part of the median loop and distensibility of the mesentery are taken into consideration. The thicker the mesentery, the less is the possibility of penetration of the loops into each other. In invaginations of the colon, any noteworthy elongation of the intussusceptum is hindered.

Mesenteric Lymph-Nodes

Etiology of Mesenteric Lymphadenitis—Infections and toxins have probably been advocated as etiological factors more than any other agents. That an actual infection of the glands themselves occur in some patients is definitely proved. Attempts to find organisms in the glands removed at operation have usually been unsuccessful, indicating that a toxin may possibly be the underlying factor in many cases. J. Ireland²²⁸ reported on 22 cases of mesenteric lymphadenitis, 20 were traced and re-examined from 60 days to 4 years after appendectomy. Sixteen of them had had no kind of abdominal distress simulating another attack of mesenteric lymphadenitis since operation, 4 were found to have attacks much like those present before operation. Bacteria may be transmitted from the throat

by the blood stream or may be swallowed and produce localized inflammatory lesions in the intestine with secondary involvement in the lymph glands. Distention, catarrhal inflammation, trauma, intestinal stasis, incompetence of the ileocecal valve with autoinfection of the ileum, regional ileitis, abrasions of the mucous membrane and lowered resistance of the surface epithelium of the intestine have been thought to be important in the production of mesenteric lymphadenitis. Allergy seemed to be the causative factor in 1 case.

A. K. Foster, Jr.²²⁹ suggested that gastrointestinal stasis and conditions attributing to it allow chronic absorption of histamine-like substances which may cause mesenteric lymphadenitis, especially when the appendix is diseased. Mead has pointed out that the total number of mesenteric lymph-nodes varies greatly, from about 30 in a premature stillborn infant to 300 or more in a full-term child. They occur in 3 definite locations. The first group is located at the last anastomosing branching of the vessels before the intestine is reached, the second group at the next larger anastomosing branches of the large mesenteric vessels, while the third group is located at the root of the mesentery where the large vessels arise. The third group generally constitute the largest lymph-nodes.

Arnold, at the University of Illinois, pointed out the great variability in size under varying conditions and stated his belief that many organisms penetrate the intestinal mucosa only to be destroyed later by the mesenteric lymph-nodes and liver, which contain the phagocytes needed for such function. Heyd recognized the great task of the liver in destroying organisms that are absorbed from the intestinal canal. W. Klein²³⁰ reporting on 140 cases believes that the cause of mesenteric adenitis is absorption of toxins

from the intestinal tract. These toxins may be of bacterial origin or may be the products of digestion. The statement that mesenteric adenitis is preceded by an infection of the upper respiratory tract is not borne out by careful histories and close observation, and is also contrary to the normal physiology of the animal body.

The fact that mesenteric adenitis is always accompanied or immediately preceded by inflammation of the intestines, as observed at operation, is further evidence that this form of adenitis is a direct result of pathological conditions in the intestines. There is, however, a small group of cases of very acute involvement in which infection of the upper respiratory tract occurs simultaneously with mesenteric adenitis. In these cases it is perhaps a general toxemia that brings the toxins to the intestines via the blood stream and causes inflammation with consequent glandular hypertrophy. In only 8 per cent of the author's series was there a history of a preceding upper respiratory infection. The average age reported by most authors is less than 20 years. S. Rosenberg²³¹ believes that there is a definite seasonal incidence, perhaps related to infection of the upper part of the respiratory tract. He reported on 75 cases.

Signs and Symptoms—The pain of mesenteric adenitis is not easily explained. A possible explanation is that inflammation and hyperplasia of the glands cause pressure on the sensory pacinian capsules in the mesenteric leaves, or perhaps these sensory organs are directly invaded by toxins. W. Klem classifies nonspecific mesenteric adenitis into 3 types according to the symptomatology. The first group is the least common and occurs in children from 6 to 12 years of age. The onset is sudden with high fever, marked toxemia and a high blood count.

The face is flushed, the pulse rapid, and the throat congested and inflamed. The abdomen is distended and tender throughout, especially in the right lower quadrant. When operated on, the whole intestinal tract, particularly the small intestines, is thickened and extremely red, and the mesenteric glands are deep pink.

The second type is most common and is often mistaken for appendicitis. However, the tender point in the right lower quadrant is at a higher level than in appendicitis and is internal to McBurney's area; and when the patient is turned on the left side, the tender area is shifted to the left and is absent on the right. This 1 sign, when present, has always differentiated mesenteric adenitis from acute appendicitis.

The third type of mesenteric adenitis described by the author gives the same history as the second, but examination of the abdomen discloses that whereas the tenderness can be shifted from right to left with change of position, tenderness over the cecum persists. This type cannot always be differentiated from a pathological process which involves the appendix.

W. E. Adams and M. B. Olney²³² cite 12 cases of nontuberculous and 1 of tuberculous mesenteric lymphadenitis. Two of the most outstanding features of this condition are the colicky nature of the abdominal distress and the marked tendency toward recurrent attacks. In the cases of one-half of the patients, the pain remained generalized over the abdomen and in only 2 was it localized in the right lower quadrant of the abdomen. Nausea and vomiting occurred in most cases, and diarrhea was present in 5. The white cell count is frequently elevated out of proportion to the patient's temperature. A rapid subsidence of abdominal symptoms and pathological find-

ings is very helpful in the determination of the true nature of the condition. The period of observation need not be longer than 2 or 3 hours but if the symptoms and findings make delay seem hazardous, exploration should be carried out at once.

Diagnosis—A definite preoperative diagnosis is difficult. The history of many previous attacks and the colicky nature of the abdominal pain, together with the lack in many cases of localizing signs and symptoms, are helpful in suggesting a definite diagnosis. Mesenteric lymphadenitis is almost always confused with acute appendicitis, and it must also be differentiated from pyelonephritis, intussusception, and Meckel's diverticulum. The condition also resembles infectious gastrointestinal disease. Mesenteric lymphadenitis is frequently the first concrete revelation of inflammation in the form of a mild or symptomless appendicitis, typhilitis, or enteritis. It is possible to develop cholecystitis or pancreas disease over the plexus celiacus through retrograde transport or propagated thrombolympangitis in mesenteric lymphadenitis of the vermiform region.

Treatment—It is probably not safe to remove a mesenteric lymph node, especially if the infection is due to the streptococcus. Appendectomy or any other procedure necessary to remove abnormalities which may have had something to do with the occurrence of mesenteric lymphadenitis is the prescribed treatment. Intestinal stasis and the conditions contributing to it allow chronic absorption of histamine-like substances which can cause mesenteric lymphadenitis should be corrected. Most patients remain symptom free following appendectomy. The *prognosis* for a permanent cure is good.

Lymphatic System

Ileocecal Lymphadenitis in Children—This condition is common in chil-

dren and young adolescents between the ages of 3 and 18 years. The symptoms are similar to those of appendicitis. The patient is seized with abdominal pain which is of varying severity and generally can be traced to the right side of the lower abdomen. During the attack there is evidence of definite toxicity. The attacks subside as a rule, and the child has intervals of weeks or months during which he is apparently well, but the attacks recur until appendectomy is performed, after which he will be free from symptoms. A. E. Brown²³³ believes that with care and a knowledge of the condition a correct preoperative diagnosis is possible in a reasonable proportion of cases.

Allergy in Diseases of Lymphatic Glands

—C. Rotta²³⁴ followed the behavior of allergy to tuberculin in a group of 700 patients who were suffering from diseases of the lymphatic glands. He determined the intensity of allergy from the intensity of the tuberculin reaction, which was done by means of an intradermal injection of 0.2 cc. of a 1 to 3 per thousand old tuberculin solution. The same dose of a 1 per 500 old tuberculin solution was intradermally injected in anergic patients. The greatest tuberculin reaction consists in the appearance of a necrotic papule at the point of the injection, which shows intense allergy. It appears in almost all cases of tuberculosis of the lymphatic glands, especially if there is caseous degeneration of the glands. It is a reaction proper to tuberculous lymphoma and to tuberculous, tracheobronchial or hilar adenopathies. The reaction is more intense when the lymphatic structures only are involved by tuberculosis than when they, as well as the lung, are tuberculous. Patients who are suffering from malignant granuloma are in a condition of anergy or

hypoanergy, except when the condition coincides with hyperplasia of the reticulo-endothelial tissues, especially of the spleen, or with tuberculosis in evolution. Patients who are suffering from tuberculous hyperplasia of Ziegler's type are in a condition of transient anergy, which changes to allergy as the adenopathies and splenomegaly disappear. In myeloid and lymphatic leukemia, lymphosarcoma and reticuloma there is allergy. In tumors of the mediastinum and the liver and tumoral metastases in the lymphatic glands there is anergy. The author concludes that in adults who are suffering from lymphopathies the presence of an intense old tuberculin reaction shows the tuberculous origin of the lymphatic condition. Anergy shows malignant granuloma, tuberculous hyperplasia and tumoral metastases. The negative results of the tuberculin reaction in children who are suffering from adenopathies indicate that the patients do not have tuberculosis.

Tuberculosis of the Tracheobronchial Lymph Nodes—Normal lymph nodes cannot be demonstrated either by the roentgenologic or by any other method. The roentgenologic demonstration of infiltration about the pulmonary hilus constitutes a definite sign of tuberculous lymph nodes. Compression symptoms of the trachea occur only in young children and then rather infrequently. Painful sensations both subjective and objective are not reliable. The tuberculin test is of considerable importance in determining the specificity of the infectious process. This is true only of the early and the preschool age. The diagnosis is justified in the presence of roentgenologic evidence of enlarged lymph nodes, the presence of extrapulmonary tuberculous lesions, an enlarged hilus shadow, the presence of oval or round shadows in the hilus with salt deposits, and the presence of perifocal infiltrations.

Clinical Aspects of Tuberculous Lymphadenitis—In 324 cases of peripheral tuberculous lymphadenitis, B. C. Thompson²³⁵ has found the supraclavicular and axillary lymph nodes affected only one-third as often as the upper cervical group. This form also showed a tendency to appear later in life, with a maximal incidence at the age of 15, compared with 9 years in the latter type. More than half of the group showed x-ray evidence of intrathoracic tuberculosis, which usually took the so-called childhood form, with 1 or more small foci in the periphery of the lung and massive enlargement of the tracheobronchial lymph nodes. Calcification was usually present in these lesions. Much less commonly the associated pulmonary disease was of the adult type, with extensive cavitation and fibrosis and no mediastinal adenopathy. By reason of its pulmonary origin and the associated tracheobronchial disease, tuberculosis of supraclavicular and axillary lymph nodes has a significance quite different from that in the nodes of the upper part of the neck. It should, of course, be remembered that tuberculosis tends to spread from 1 group of lymph nodes to the next, by either normal or retrograde paths. Those unusual cases in which tuberculosis involves simultaneously the upper cervical and tracheobronchial lymph nodes, between which there is no direct anatomic connection, are probably due to concomitant infection of both the upper and the lower parts of the respiratory tract.

Treatment—Tuberculosis of Cervical Lymphatic Glands—R. Reid and M. C. Wilkinson²³⁶ outline a method of treatment in 119 cases. The treatment consisted of a combination of constitutional and operative measures; but constitutional treatment has been the fundamental factor, and in no case was surgical extirpation of the tuberculous glands

adopted as a primary measure. The cases were divided into 3 groups: (1) Enlarged glands with periadenitis; (2) enlarged glands without periadenitis, and (3) cases of residual infection following natural or artificial attempts at cure. Tuberculous lymphadenitis may be regarded as a local tuberculous lesion in a patient whose resistance to the disease is insufficient. Constitutional treatment, therefore, is of paramount importance to prevent progress or recrudescence of the disease. The chief factors in constitutional treatment are *rest* (restraint from all activity), *open air*, a *liberal balanced diet* with an adequate supply of *vitamin* and *heliotherapy*. Tonsillar and pharyngeal sepsis in the pathology of tuberculous glands of the neck is of utmost importance.

The treatment of a tuberculous abscess arising from a gland depends on whether superadded secondary infection has occurred or not. If there is secondary infection the pus should be evacuated by incision, and free drainage should be established. If there is no secondary infection an attempt should be made to treat the abscess by aspiration. The success of aspiration depends on the employment of a technic in which the needle is passed into the cavity of the abscess through and across muscle. The route of the needle is thus closed by the approximation of the muscular fibers.

The operation for radical excision of tuberculous glands of the neck is a controversial field in surgery. The main contraindication for the operation is active disease with periadenitis. The Group 1 cases treated by conservative means required on an average 6.7 months to complete a clinical cure, and 24 of 29 gave a good result on discharge. The operative 45 cases were under general treatment for an average period of 2.9 months before they passed from this

group to Group 2 or 3, and were then ready for operation. After operation 1 month of treatment was given to allow satisfactory healing of the wound. There were good results in all the operative cases. Satisfactory results were obtained in the 6 cases in Group 2 under constitutional treatment. They were retained in the sanatorium for an average period of 3.25 months. The 16 cases treated by operation all gave good results and were kept under constitutional treatment for an average period of 2 months before operation. The statistics of the 13 cases in Group 3 give no useful information, as the group contains such a variety of cases of residual infection that no generalization can be made about them. But the immediate results following treatment in all groups were good except in 5 cases of Group 1. Ten patients did not complete the treatment. It is the authors' opinion that the nasopharyngeal lymphatic tissue is the probable path of entry for the tubercle bacillus in this disease. Tuberculosis of the cervical lymph glands is a local disease which does not give rise to metastatic lesions.

W. Matheja²³⁷ demonstrates that in all nonspecific inflammations of the cervical lymph nodes the results of short wave treatments are more rapid and more reliable than is the case in any other form of treatment. No difficulties are encountered in the ambulatory treatment of the glands. The main effects of the short wave treatment are rapid disappearance of pain and fever, improvement in the general condition and cure. The course of the process of recovery is dependent on the duration of the glandular inflammation. New glandular swellings, in which the treatment of short waves is begun early, are quickly absorbed. Cases of adenitis that have existed for longer periods break down

more rapidly under the influence of the short waves and can be subjected earlier to surgical treatment. In the presence of chronic nodules of the cervical lymph nodes and in case of specific, particularly tuberculous, adenitis, the treatment with short waves is ineffective.

The Lymphoid Tissue of the Alimentary Canal

H. G. Thompson²³⁸ stresses the apparent relation of the position of these places of lymphoid tissue to bacterial infection. Thus, the tonsillar lymphoid ring is at the entrance to the pharynx, where the path of the food and the path of the inspired air cross one another, *i. e.*, the point where the maximum possible combined air-borne and food infection may occur. Peyer's patches are situated where the curbing antibacterial action of the gastric juice and the bile begins to lose its power and micro-organisms begin to multiply. The vermiform appendix with its lymphoid tissue is situated at the apex of the cecum at the point where there is probably the greatest stagnation of broken-down food-stuffs and where bacteria are most able to multiply. The solitary follicles of the large intestine are likewise in a position where there is marked fermentation and bacterial action. It is at the lymphoid ring at the back of the throat and nose that bacteria are taken in by respiration and food. For the most part they are swallowed and then destroyed by the acid gastric juice, but before entering the esophagus they have incorporated with them the salivary corpuscles, which are the lymphocytes discharged by the lymph follicles of the tonsils. The author suggests that possibly the discharged lymphocytes or salivary corpuscles react to the bacterial toxins and supply a dose of immune bodies which are swallowed and

absorbed by the alimentary canal and help to establish immunity in this manner.

The author touches on the matter of tonsillectomy, and states that a few years ago it was the fashion for children to have their tonsils removed on the slightest pretext. Now it is being realized that healthy tonsils must have some use and that simple enlargement, so long as it is not causing obstruction to respiration is due to the response of the body to some lack of hygiene or to some dietetic deficiency. The author quotes Layton, speaking from a large clinical experience, that in children under 5 to 8 years of age removal of the tonsils impairs resistance to infection. He cites other instances in support of the theory that the lymphoid tissue of the tonsillar ring is associated with the protection of the young subject from bacterial infections and to substantiate the fact that it is of value in the economy of the growing child.

With regard to the relation of the intestinal lymphoid tissue to bacteria, there seems to be definite evidence that such a relation exists. From a large number of experiments which the author conducted with rabbits, he was able to determine that there is a regular flow of cells from the lymphoid tissue into the lumen of the alimentary canal and that these cells are almost entirely small lymphocytes. His next effort was to attempt to discover what the reaction of the lymphoid tissue to pathogenic bacteria was. For this purpose cultures of (1) bovine tubercle bacilli and (2) staphylococcus aureus were used in a series of experiments on 9 rabbits. The results suggest that bacteriolysis takes place either in the lumen of the bowel or in the lymphoid tissue; also that bacteria may pass rapidly through the lymph follicles. Results were most marked in the appendix. The effect of deficiency

in vitamin A was also studied. Several batches of rabbits were put on a diet deficient in vitamin A. In the rabbit the lymphoid tissue of the alimentary canal is normally associated with the presence of gram-positive bacteria. It became obvious that the diet deficient in vitamin A produced a marked increase in the number of organisms in the lymphoid tissue. Not only were they present in large numbers scattered throughout the deeper follicles, but they appeared to be massed in colonies as if they were multiplying locally. Especially was this the case in the lymphoid tissue of the vermiform appendix. Moreover, the lymphoid follicles began to show signs of atrophy when the animals had been deprived of vitamin A. In the later stages the animals began to develop signs of xerophthalmia, and it was in these cases that the lymphoid follicles were represented by only a very thin layer of leukocytes. These findings were so marked that it was decided to try to determine if the readministration of vitamin A would cause a regeneration of the lymphoid follicles. Accordingly, a rabbit was chosen which had been on a diet deficient in vitamin A for several months, and in which xerophthalmia was well developed. The animal was given a similar diet with the addition of carotene in oil for 1 week. It was then killed and the appendix and other lymphoid organs were removed for histological study. It was found that the deeper follicles showed the characteristics of active regeneration with both superficial and deep follicles present.

PERITONEUM

Peritoneoscopy—E. B. Benedict²³⁹ has made 48 examinations with the Rud-dock peritoneoscope. There has been 1 fatality, in which pneumoperitoneum may

well be considered as a contributory cause of death. The patient was in the terminal stages of multiple lung abscess, coronary disease and possible echinococic cyst of the liver. No real errors in diagnosis have occurred. When patients are carefully selected, peritoneoscopy is attended with little risk. Those with serious pulmonary or cardiac disease are not good prospects. Abdominal adhesions may complicate the procedure, but by careful selection of the site of puncture difficulties have thus far been avoided. Peritoneoscopy may be indicated in any abdominal or pelvic condition in which the diagnosis is obscure or in which additional evidence is needed to confirm a diagnosis or to plan treatment. The procedure will frequently give information that will decide for or against laparotomy.

Peritoneoscopy is useful in cancer, cirrhosis, tuberculous peritonitis, ascites, pelvic tumors, ectopic pregnancy and ovarian dysfunction. In 1 case an excellent view was obtained of a polycystic liver, in another case of supposed echinococic cyst the liver was found to be normal, and in a third case in which there was a questionable palpable mass the peritoneal cavity was found to be normal.

Serious cardiac or pulmonary disease may be a contraindication, for the peritoneal distention necessary for a satisfactory examination may somewhat embarrass the circulation and the diaphragmatic movements. Because of the danger of spreading infection, peritoneoscopy is contraindicated in inflammatory conditions. Peritoneoscopy will not replace exploratory laparotomy in all cases, but in certain cases it makes it possible to avoid major surgical operations. Peritoneoscopy requires local anesthesia, a stab incision and hospitalization of 1 day.

Tumors of Retroperitoneal Space

In 1929 E. Hesse²⁴⁰ described a triad of symptoms of retroperitoneal tumors and their influence on the sympathetic nerves of the corresponding lower limb. These symptoms are lowering of the temperature, excessive sweating and, during the period of nervous excitation, exaggerated pilomotor reflex in the lower limb which corresponds to the side of the tumor. During the period of advanced destruction, when the sympathetic nerve is either inhibited or paralyzed, the temperature of the limb is again increased, the sweating stops and the pilomotor reflexes are arrested. These symptoms are important when the tumor is in its early stage during which the diagnosis and the localization of the growth can be made with no other methods. The difference in temperature is best measured at the toes or at the back of the foot. By merely laying the hand on both feet, the difference in temperature can often be made out easily. For more minute comparisons, comparative thermometry will have to be applied. By means of this method it is possible to tell whether the process is in its initial or its advanced stage. The temperatures of both limbs are traced daily and the day on which the 2 temperatures are the same indicates the passage from the state of nervous excitation to that of inhibition or paralysis. The author named this crossing "calorimetric scissors." These symptoms are verified on 8 patients, in some of whom the difference of temperature was often more than 5 degrees and well noticeable to themselves.

Torsion of the Omentum

The predisposing factors are abnormal bulkiness and weight of the omentum, and adhesions along its free border, which cause a drag and lead to pedun-

culation. These factors are present especially in cases of hernias containing omentum, and torsions of omentum are therefore often combined with epiplocele. Acute inflammatory processes can also be the cause of torsion, though probably only when pedunculate extensions, which are not uncommon in the right part of the omentum, already exist. Other factors are abnormal shapes of the omentum; congenital malformations and torsions; inguinal hernia, especially on the right side; postoperative or idiopathic inflammatory processes which tend to alter the form, weight, and consistency of the omentum; tumors and cysts; changes in organs which are anatomically related to the omentum, such as ptosis of the spleen, ovarian cysts, uterine fibroids, inflammatory processes of the female adnexa, and appendicitis, and, finally, adhesions of the omentum to the abdominal wall or to the intestine itself.

The usual distinction, and probably the best from a clinical point of view, is between (1) torsion only in the hernial sac, (2) torsion both in the hernial sac and in the abdominal cavity, and (3) torsion without hernia, (*a*) unipolar, (*b*) bipolar. Torsion of the omentum has been correctly diagnosed before operation in only a very few cases. If the abdominal symptoms predominate, the case is diagnosed as acute abdominal disease, usually as appendicitis, if the hernial symptoms predominate, the case is judged to be one of incarcerated hernia.

S. O. Jonsson²⁴¹ calls attention to the danger of confusion, in the former case with appendiceal abscess, and in the latter with incarcerated hernia; and warns especially against the danger of error when the torsion is double, with 1 spiral in the hernial sac and another proximal to this, at the place where the omentum

is adherent to the colon. The other 6 cases related by the author belong to the group of simple abdominal torsions. The cause in 1 case was hernia, although at the operation the hernial pouch was found to be empty; in another it was lymphangioma in the omentum; in a third possibly acute appendicitis; and in the remaining 3 cases the condition was idiopathic. In connection with 1 of the cases, the author briefly discusses the similar disease, torsion of the epiploic appendages. He calls attention to the fact that torsion of the omentum can give rise to a more chronic pathological picture, with recurring abdominal pains suggesting chronic appendicitis.

M. Mauro²⁴² reports the case of a 40-year-old man with a right inguinal hernia which always could be easily reduced. The presenting complaints and clinical findings included pain in the right iliac fossa, abdominal rigidity, the presence of a fixed mass on palpation, and elevation of the temperature. A tentative diagnosis of acute appendicitis was made, but laparotomy revealed an acute torsion of the greater omentum. The peduncle was ligated and the omental mass was resected. Uneventful recovery followed. The second case observed by Mauro was that of a 50-year-old man who for the past year presented a left inguinoscrotal hernia. When seen at the clinic he complained of severe pain in the left iliac fossa. On operation an acute torsion of the omentum was found. The figure shows the omental mass which was about the size of an orange with a peduncle which was twisted counterclockwise. The mass was adherent to a loop of intestine which was also twisted and formed a true volvulus. After disengagement of the intestinal loop and resection of the twisted omental mass the patient made an uneventful recovery.

PERITONITIS

Anatomy—The routes of spread of free fluid coming from a perforated viscus within the peritoneal cavity are described by C. G. Pantin²⁴³ as: (a) From a perforated duodenal ulcer to the right flank and right diaphragm with right shoulder pain; (b) from a high gastric ulcer to the left flank and diaphragm, with left shoulder pain usually appearing later than the abdominal pain; (c) from a gastrojejunal ulcer along the right side of the mesentery into the right lower quadrant; (d) from a ruptured ectopic pregnancy through either flank to the diaphragm; (e) from a ruptured spleen to the left diaphragm, with pain first in the shoulder and then in the flank. L. Allen^{243a} has photographed frogs' red corpuscles entering stomas in the diaphragms of mice after intraperitoneal injection. He was not able to demonstrate stomas anywhere except in the diaphragm, and is of the opinion that they are open when the diaphragm is relaxed, and are closed by the contraction of this muscle.

This work is partly confirmed by the observations of B. Menkes,²⁴⁴ who injected a colloidal suspension of thorium dioxide into the peritoneal cavity of guinea pigs and rabbits, and took x-ray films at various intervals. It is generally accepted now, according to J. S. Horsley,²⁴⁵ that the capacity for absorption from the peritoneum, so far as its histologic structure is concerned, is about the same everywhere. Even though the diaphragmatic peritoneum has no more capacity for absorption than the peritoneum elsewhere, the movements of respiration—the contraction and the relaxation of the diaphragm with the liver beneath it—may act somewhat as a pump and mechanically force exudate into the peritoneum more rapidly than it would

be absorbed without such alternate compression and relaxation.

Physiology—1. *Absorption of Solutions and Particulate Matter*—Absorption occurs both through the lymph vessels and through the blood vessels but probably it is much greater through the latter. The lymphatic duct is primarily a collector of material from the intestinal lacteals and carries nutrient material, while the lymphatics of the peritoneum itself empty into the lymph nodes and not directly into the thoracic duct as the lacteals do. A. J. Schechter²⁴⁶ believes that, in the uninflamed peritoneal cavity, the laws of diffusion and osmosis govern the absorption of substances other than proteins. The mechanism of the absorption of proteins is not yet established. When normal saline, glucose, or salt-bicarbonate solutions were injected into the peritoneal cavity, they all gradually took on the electrolytic composition of edema fluid and were absorbed at a constant rate. H. A. Mengle²⁴⁷ found that the absorption of particulate matter was more rapid under ether anesthesia than under sodium-amytal or local anesthesia.

2 Experiments indicate that absorption of bacteria and other particulate matter commonly occurs by way of the lymphatics, and of solutions or even large molecules by way of the blood stream. Whether the latter enter the lymphatics first is not known, nor is the method of passage of any substance from the peritoneal cavity to the lymph or blood stream explained. It seems established that the inflamed peritoneum absorbs usually less actively than the uninflamed and that substances in solution are absorbed best when isotonic.

3. A number of authors have studied the cellular reaction of the peritoneum to the injection of various substances. All are agreed that the polymorphonu-

clear leukocytes are normally present in very small numbers, the chief cells in the normal peritoneal fluid being large phagocytic mononuclear cells.

4. Experiments show that almost any substance injected into the peritoneal cavity of animals slowed peristalsis, and electrical or mechanical stimulation of almost any part of the parietal peritoneum caused a reflex slowing of peristalsis, which could be prevented by cutting of the splanchnic nerves or by cutting of the cord at the second dorsal segment. After ligation of the blood vessels, stimulation of the splanchnic nerves produced no change in peristalsis, which suggested that the reflex passes through the sympathetics in the walls of the blood vessels. H. Imanaga²⁴⁸ believes that the lower blood pressure in diffuse peritonitis and the subsequent slowing of the blood stream cause an accumulation of acid in the intestinal wall which is responsible for atony of the gut and loss of peristalsis. When he examined the blood of the portal vein in animals with diffuse peritonitis, he found a lower pH, a lower sodium chloride content, and a marked lowering of the oxygen content. A number of authors have studied the blood chemistry in peritonitis, and it was found that the blood sugar was increased in proportion to the degree of peritonitis, and that the adrenalin content of the blood and also of the adrenals was promptly elevated. M. Tabanelli²⁴⁹ found in 33 patients with acute peritonitis a fall in blood cholesterol, which continued progressively in those who died, but the cholesterol returned to normal in those who recovered. M. Okada²⁵⁰ thinks that histamine is probably the important factor in death from peritonitis.

Toxicity of the Peritoneal Exudate—G. S. Bergh, W. F. Bowers, and O. H. Wangenstein²⁵¹ perforated the

stomach in 2 series of dogs, 1 with, and 1 without, a full stomach. Of 29 dogs with an empty stomach, only 2 died. Of 30 dogs recently fed, 26 died. Of 17 dogs perforated immediately after the ingestion of fluid only 3 died. Of 16 dogs with a perforated duodenum 12 died, and of 9 dogs with a perforated jejunum 4 died. Of 9 dogs with a perforated lower ileum, all died. Of 7 dogs with a perforated cecum, 2 died. Of 8 dogs with a perforated rectum, 1 died. These findings confirm the observations of previous authors that the lower ileum is the most infective part of the gastrointestinal tract.

H. A. Mengle, N. F. Paxson and J. O. Bower²⁵² induced spreading peritonitis in 20 dogs which had previously been immunized against *Clostridium welchii* toxin, in order to ascertain what proportion of the animals so immunized would survive the infection. The marked drop in mortality in this group as compared with the control group leads one to believe that the toxemia accompanying spreading peritonitis may be largely produced by the toxin of *Clostridium welchii*.

Bile Peritonitis—H. N. Harkins, P. H. Harmon and J. E. Hudson²⁵³ estimated the exudation to be approximately a third of the blood volume and 60 per cent of the plasma volume, with resultant marked hemoconcentration. They believe that death is due to this, rather than to the activity of bacteria which appear later. V. H. Moon and D. R. Morgan²⁵⁴ concluded that bile caused an increased permeability of the capillary walls. S. H. Mentzer²⁵⁵ concludes that human mortality depends always entirely on whether the bile is infected or not. M. H. Manson and C. T. Eginton²⁵⁶ from their experiment, conclude that there are at least 2 factors causing death in bile peritonitis; the primary

injury to the peritoneum by the toxic bile salts and the secondary shock from the loss of fluid from the vascular system.

Bacteriology—K. Roberts, W. W. Johnson and H. S. Bruckner²⁵⁷ obtained positive cultures in 76 per cent of their cases, in which the peritoneum was opened in clean operations; however, these organisms were practically the same as those which they obtained from the deep layers of the skin and in the laboratory air. R. Friedrich and H. Weber²⁵⁸ demonstrated many intestinal organisms in stomachs afflicted with carcinoma, while stomachs or duodenums with benign ulcers were shown to have very few organisms and the cultures were often sterile. Therefore the higher incidence of peritonitis following resection of the stomach for carcinoma as compared with gastroenterostomy for ulcer. Several authors have reported cases of acute peritonitis which yielded the enterococcus in pure culture. H. Mundorff²⁵⁹ reports on 33 cases of pneumococcal peritonitis. She found a predominance of children from rural districts, most of the patients were girls. Of the 33 cases, there were 17 with an acute onset. Nine of the 17 patients died. In the 8 that recovered, complications such as pneumonia, nephritis and late abscesses developed. The aspects of secondary pneumococcal peritonitis, which develops in the course of other pneumococcal infection, are quite different from those of the acute or primary forms.

Tuberculous Peritonitis—Since the favorable results of operation in tuberculous peritonitis are out of proportion to the amount of surgical work performed, there must be some other explanation of why these patients improve. It seems likely to M. J. Brown²⁶⁰ that in some cases equivalent improvement may be accomplished by the use of closed ether anesthesia alone. A temporary

anoxemia produced by the anesthesia might be an explanation for the apparent cures. The tubercle bacilli are known to be anaerobic organisms. From the known facts of culturing the tubercle bacilli, the reduced oxygen intake of the body would explain, at least partially, the improvement that follows when ether anesthesia alone is administered.

Pneumoperitoneum in Perforations of Gastrointestinal Tract—J. R. Paine and L. G. Rigler²⁶¹ report on 62 proved cases of perforation of the stomach, duodenum, small intestine and colon, 47 of the patients were given x-ray examinations, and gas outside the gastrointestinal tract was observed in 78.8 per cent. In 38 cases of perforation of the stomach or duodenum, free gas was observed in 28 cases.

G. Lenarduzzi²⁶² discusses the roentgen picture of encapsulating peritonitis. The small intestine shows a piling up of almost all its loops which depends upon the extensiveness of the process. A sausage-like mass is thus produced which is well delimited from the normal residual portion of the small intestine and also from the stomach and colon. The piling up of the intestinal loops may leave their aspect unaltered, but if the capsule becomes adherent to the visceral peritoneum, the individual loops are approximated and the entire mass may suggest the presence of greatly dilated intestinal loops equal in caliber to those of the colon. In addition the mass may appear segmented and give a pseudo-colic effect (Vespignani's sign). The latter sign is characteristic in advanced cases. With the aid of pressure the mucosal valves may be visualized also and this is of great aid in establishing a differential diagnosis.

Treatment—Prophylactic Treatment—1 *Vaccines*—The purpose of administering these substances is not to

effect a true vaccination in the sense of obtaining general constitutional immunity but to increase the local resistance of the peritoneum by bringing about a heavy influx of phagocytes, chiefly the polymorphonuclears. The value of these so-called vaccines has not been definitely determined. The most active workers in this field have been B. Steinberg and H. Goldblatt.²⁶³ Barger at the Mayo Clinic had developed a vaccine made from colon bacilli and streptococci, where it was given as one of the several pre-operative measures before resection of the intestine.

2 *Bovine amniotic fluid*, which has been concentrated, has been recommended as a preventive of both post-operative adhesions and peritonitis when given intraperitoneally.

3 *Filtrates or Antivirus*—The use of *coli antivirus* in a few human beings showed no convincing evidence of benefit. It seems true that some protection against organisms injected into the peritoneal cavity can be evoked by the previous injection of filtrate or antivirus, but this effect may be due to nonspecific irritation of the peritoneum.

4 *Bacteriophage*—In mice, H. Z. Jern, H. D. Harvey and F. L. Meleney²⁶⁴ obtained protection with intraperitoneal injections of *bacillus coli bacteriophage* against *bacillus coli* peritonitis, amounting to 25 times the dose of organisms that killed controls. There is little or no evidence that commercial preparations of single or combined bacteriophages have proved their value in the prevention or cure of peritonitis. If it can be determined that the peritonitis is caused solely or chiefly by a hemolytic streptococcus, treatment with *sulfanilamide* should benefit.

Active Treatment—1 *Operative Treatment*—Most authors believe in

prompt operation in most cases of peritonitis, with removal of the focus of infection with a minimum of trauma. In the case of appendicitis some surgeons recommend that the appendix should always be removed, while others advise not removing it in the case of abscess or general peritonitis if it cannot be excised without the danger of spreading the infection. J. W. Kennedy²⁶⁵ believes the watchful waiting of the physiological surgeon for a quiescent stage in the peritonitis abdomen due to a perforated appendix has been a disastrous blunder.

R. D. McClure and W. A. Altemeier²⁶⁶ found that the lowest mortality in appendicitis occurred in the cases operated on through a McBurney's incision and that spinal anesthesia was accompanied by a lowered death rate than ether. E. S. Jones²⁶⁷ explained his good results as being due to a cecostomy through the appendix stump. J. S. Horsley²⁴⁵ advises **suction** to remove pus or exudates; gauze should not be placed within the peritoneal cavity, and on no condition should the pus or exudate be sponged away. The stump of the appendix should be treated by tying it and disinfecting it; it should not be buried. Nothing is given by bowel or by mouth; water, electrolytes and calories are supplied by **continuous intravenous injection** of 5 per

cent **dextrose in Ringer's solution**, and by hypodermoclysis of $2\frac{1}{2}$ per cent solution of **dextrose in physiological saline**. There is a difference of opinion in regards to drainage. W. Wayne Babcock has been using glass drains with success.

2. General Treatment—It is important to give nothing by mouth after operation but restoring the water, calorie and electrolytes by parenteral administration. A few favor **frequent transfusions of blood**. **Fowler's position** is generally accepted and **gastric suction** through a nasal tube is rapidly gaining favor. **Morphine** is advocated by most authors. Potter gives **pitressin** after operation.

A great deal of interest has been aroused by the report of Hans Havlicek,²⁶⁸ who in 1932 reported the treatment of 108 cases of peritonitis following appendicitis without a single death. Havlicek uses the "Laparophoslampe" with a Wood's filter which gives essentially a monochromatic light permitting line 366 to come through. This light is luminescent, and the visible rays and those which produce erythema and conjunctivitis are filtered out. Sections of bowel, mesentery and omentum are exposed to the lamp for a period of 5 to 25 minutes, depending upon the severity of the condition.

HERNIA

By FREDERICK A. FISKE, M.D.

Diaphragmatic Hernia

From the standpoint of etiology, diaphragmatic hernia should be divided into 2 groups, the congenital types and the traumatic types.

Congenital—According to Donovan,²⁶⁹ the most common sites of defects in the diaphragm are: The foramen of

Bochdalek, the foramen of Morgagni, the dome of the diaphragm; and the esophageal hiatus. It is said that a hernia through the aortic or vena caval openings has never been reported. The embryonic diaphragm consists of 2 parts. A ventral part which is the cephalic portion of the septum transversum, develop-

ing in the cervical region, and a dorsal part which is the pleuroperitoneal membrane, developing from the lateral body walls and destined to become the closing membrane between the pleural and peritoneal cavities. During development, the diaphragm migrates from the region of the third cervical vertebra to its final location opposite the twelfth thoracic vertebra, and during this migration the plane of direction changes. It is thought that the communication between the pleural and peritoneal closes about the third intrauterine month. If this communication remains open, there is formed a pleuroperitoneal hiatus known as the foramen of Bochdalek. Since the liver lies over the right foramen, hernias at this point are less common than on the left side. Failure of fusion of the costal and sternal fibers at either side of the sternum results in the formation of the foramina of Morgagni. Failure of fusion of the elements at the dome is given as the explanation of this type. Hernia through the esophageal hiatus has been attributed to failure of development of the diaphragm at this point or to failure of migration of the stomach because of a short esophagus.

A report of 10 cases of congenital diaphragmatic hernias was made by Donovan. Seven operations were performed on 6 of these cases; all but 1 was under 6 months of age at the time of operation. Two patients died of shock, 1, a 5-week-old infant who developed a high intestinal obstruction, and the other a boy, aged 8, died after a long and tedious dissection of structures adherent in the chest and closure of 2 diaphragmatic defects. One case of esophageal hiatus hernia has a partial recurrence due to a short esophagus, but he is doing well. One patient operated at 5 months had an operation for recurrence at $2\frac{1}{2}$ years old, which has remained successful 2 years later.

One case with hernia through the left foramen of Bochdalek is well 7 years after operation. One with hernia through the left foramen of Bochdalek is well 6 years later. In 5 there were no other associated congenital defects, 2 were mongolian idiots, 1 had congenital heart, 1 cleft palate, 1 an umbilical hernia, bilateral cryptorchidism, penile hypospadias, hypertelorism, and a pilonidal sinus.

Heller and Löw-Beer²⁷⁰ report the case of a boy, aged 7, who had been subject to colic attacks since early childhood. On the basis of roentgenologic examination, a diaphragmatic hernia in the region of the left Lavey's cleft with a loop of the distal transverse colon and dextra position of the heart was found.

Traumatic—Injuries to the chest wall associated with fractured ribs and penetrating wounds in the region of the diaphragm should lead to the suspicion of this type of hernia. Mast and McDonough²⁷¹ report the case of a boy, aged 13 years, who had an accidental gunshot wound in the upper abdomen and lower thorax. He was treated conservatively for 2 weeks and discharged. Eight months later he died of an intestinal obstruction. At autopsy the entire stomach and 18 inches of the midportion of the ileum were found in the left thoracic wall. In this case the initial diaphragmatic injury was overlooked.

Hiatal Hernia—These hernias at the esophageal hiatus are usually divided into 3 types. Congenital short esophagus, the paraesophageal; and the gastroesophageal. Moersch²⁷² studied 267 cases of diaphragmatic hernia and found 246 were of the hiatal type while 25 were traumatic and 6 were the congenital type, of these, 133 were in women and 113 in men. The average age was 55 years; the youngest was 8 years and the oldest 82 years—clinical symptoms attributable to the hernia were present in all but 19

cases. Esophagoscopic findings of the various types are discussed. Operation is indicated on the basis of the severity of symptoms; of the 246 cases, 64 were subjected to operation.

Eisen²⁷³ feels that abdominal distention plays an etiological part in the production of these hernias. For this reason women who have multiple pregnancies, obesity and constipation, have them more frequently. In 33 cases encountered in the course of 1138 routine gastrointestinal examinations, 22 were females. The average age was 53 years, the youngest 25, and the oldest 78.

Symptoms—According to Harrington and Kirklin,²⁷⁴ the symptoms of diaphragmatic hernia are usually progressive and vary in type and intensity, depending on the amount and type of herniated abdominal viscera and the degree of mechanical interference with the normal function of the diaphragm, heart and lungs. The symptoms often resemble those of other organic diseases of the abdomen and thorax, especially cholecystitis, peptic ulcer, cardiac disease, secondary anemia and esophageal obstruction.

The symptoms of paraesophageal hernia begin at birth or any time in life. At the onset there is mild epigastric distress projected through to the back usually after a heavy meal. The attacks are similar in character but vary in intensity depending upon the amount of stomach incarcerated. Belching and vomiting which are usually attributed to cholecystitis bring relief. As more of the stomach becomes incarcerated, the pain may be agonizing, projected straight through to the back and up between the shoulder blades. Belching and vomiting are interfered with due to cardiospasm or pressure on the esophagus. Palpitation, tachycardia, and dyspnea are the common thoracic symptoms. Angina pectoris has

been confused. Hemorrhage is not common and usually indicates fixation of the stomach with erosion or ulceration of the mucous membrane resulting from forced vomiting.

The symptoms of traumatic hernia or congenital hernia in which the stomach alone is involved are similar to those mentioned. Usually these hernia have larger openings and contain large and small bowel, liver and spleen. The symptoms of traumatic cases are rapid in progress, severe in character, and are attributable to mechanical interference with function of the herniated viscera, as well as marked interference with the heart and lungs.

Diagnosis—All authors are agreed that the diagnosis is made only by careful radiological studies. Unger and Poppe²⁷⁵ feel that a close relationship between clinician and radiologist is essential. Unusual epigastric distress in a pregnant woman, gurgling, splashing, or rumbling sounds in the chest, especially if exaggerated in the knee-chest posture, respiratory delay or persistent cyanosis in an infant, and secondary anemia with atypical physical signs at the base of left chest should arouse clinical suspicion. The radiologic aspects from the standpoint of positions, various organs in stomach, colon, kidney, should be considered. The radiologic examination should demonstrate the type and site of herniation, the contents of the hernia, the reducibility, the length of the esophagus, the site of esophageal hiatus, the diaphragms, costophrenic spaces and associated pathology. The following findings are considered especially valuable. Persistent absence of the gas bubble in stomach; inspiratory elevation of one side of diaphragm, especially if there is a megacolon, visualization of shadows resembling stomach or intestines above the

diaphragm, especially if heart is displaced; and benign stenosis of the lower part of esophagus.

Treatment—The only treatment of a diaphragmatic hernia which will prevent serious complications and assure relief of the symptoms is the **operative reduction** of the contents and repair of the opening in the diaphragm. Harrington

cases. Ethylene or cyclopropane given under positive pressure is the preferred anesthetic. The surgical repair may be accomplished by the abdominal or thoracic route or the combination of both. For the left-sided hernias the left oblique abdominal incision is preferred, while the thoracic approach is preferable for the right-sided hernias. The exposure of the

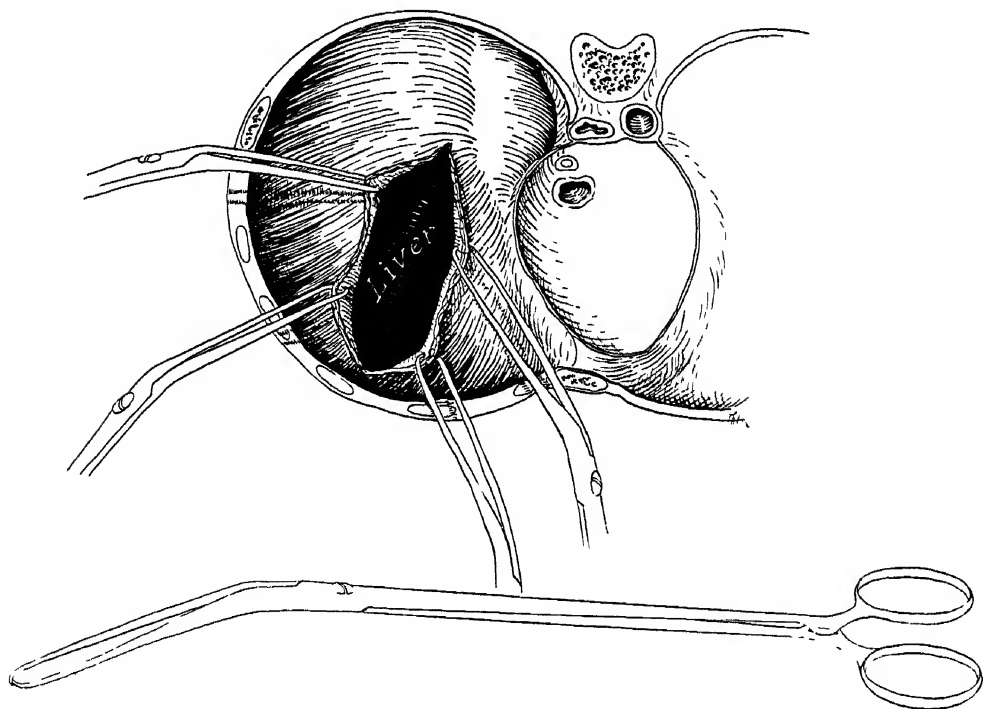


Fig 1—Upward traction on the edges of the rent by Lower's hooks as an aid in reducing diaphragmatic hernia via the chest approach (Courtesy, *Annals of Surgery*, Jan, 1938)

and Kirkland²⁷⁴ feel that a hernia through the esophageal hiatus is the only type which can be safely treated conservatively. However, in the presence of progressive symptoms even these demand radical surgery if the general condition permits. In acute traumatic cases without visceral injury it may be advisable to delay operation until the initial shock is overcome, then operative closure to prevent intestinal obstruction. **Interruption of the phrenic nerve** is a valuable aid to the surgical repair, and is used as a palliative measure in the inoperable

left hernia through the abdomen is facilitated by dividing the suspensory ligament of the liver and retracting the left lobe. The spleen is separated by blunt dissection and should be removed if severely traumatized. The paraesophageal hernia, which is the most common type in adults, has a sac which must be completely removed or permitted to retract into the posterior mediastinum. Closure of the opening is usually to the left of the esophagus, sometimes on both sides, and rarely posterior closure. Fascia lata sutures are used for the closure. A stom-

ach tube should be placed through the esophagus before closure is completed

Of 131 cases operated upon, 64 had a temporary or complete phrenic paralysis preliminary to operation, and 11 as a palliative or a therapeutic test. In 120

type of gastric resection for a gastric ulcer high on the lesser curvature was done in 1 case. In 1 case a gastroenterostomy for a large duodenal ulcer was performed. The spleen was removed in 2 cases. An appendicostomy for marked

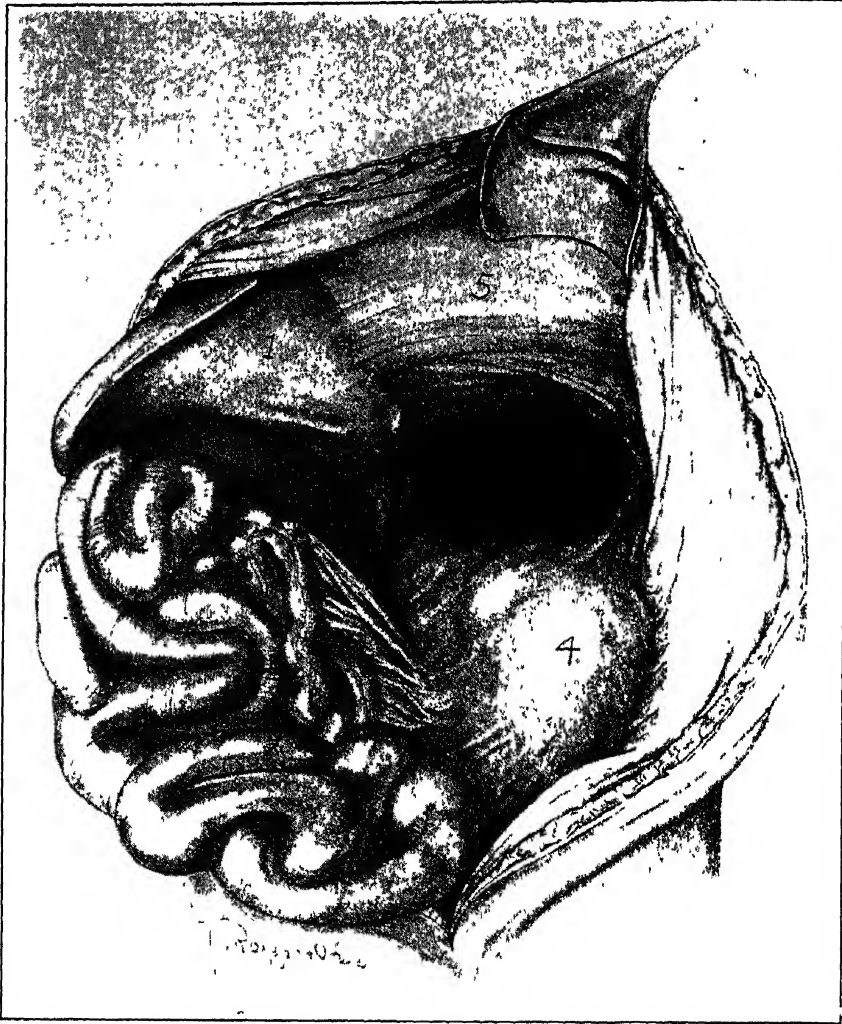


Fig. 2—After displacement of the intestines and spleen from the thorax, showing the defect in the diaphragm and the expanse of renal tascia. 1, Liver, 2, spleen, 3, stomach, 4, renal tascia, 5, diaphragm (Surgery, Jan, 1938)

cases the herniated abdominal viscera were replaced in the abdomen, and the abnormal opening in the diaphragm repaired. In 2 of these cases a combined thoracic and abdominal approach was used, and in the remaining 118 the abdominal approach was used. A Polya

dilatation of the colon was done in 1 case. Moderate congenital shortening of the esophagus was encountered in 10 cases. Twenty-one patients had previous operations without relief of symptoms. There were 7 deaths, 5 in cases of congenital hernia and 2 of the traumatic type,

4 deaths occurred in 72 hours of cardiac and respiratory failure, 3 in the second week of pneumonia. Of the 11 patients treated by palliative interruption of the phrenic nerve, 5 died, 1 of angina, and 4 all over 70 years of causes unknown; the remaining 6 have had partial relief of symptoms. Of the 113 patients who recovered from radical operation, 110

ward traction on the edges of the rent by Lower's hooks (Fig. 1).

Weinberg²⁷⁷ has found that renal fascia is of great value in closing large congenital diaphragmatic defects. A lateral abdominal incision along the inferior costal margin from the sternum to the longitudinal muscles of the spine is made. The reduction of the intrathoracic ab-

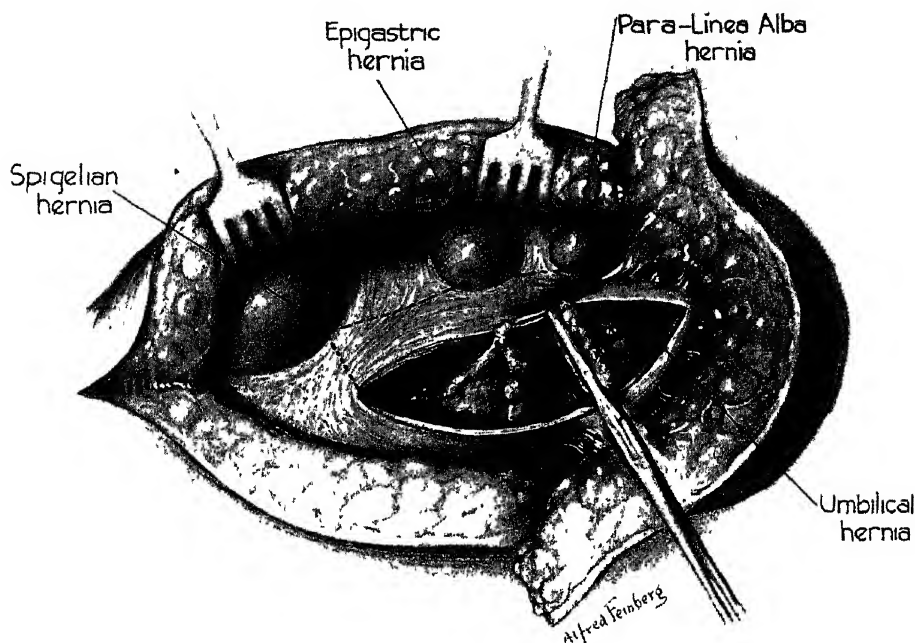


Fig. 3—Elliptical incision retracted showing the incised ring of the umbilical hernia and the amputated omental contents. The spigelian, epigastric and paralinea alba hernias are visualized. The broken line indicates the incision made in the fascia to join the 4 hernial rings (Courtesy, *Am J Surg*, Nov., 1938)

have been completely relieved and 3 have had a recurrence of the hernia and symptoms.

Sloan²⁷⁶ feels that parasternal hernia which may invade either or both pleural cavities are best approached from within the abdomen. For all other types of hernia, the thoracic approach is advised. An interesting traumatic hernia of the right diaphragm with small and large intestine, liver, and stomach in the pleural cavity is described. Reduction of the contents was greatly facilitated by up-

dominal viscera is aided by introducing a $5\frac{1}{2}$ -inch rubber tube into the thorax to overcome the negative pressure induced by respirations. Positive pressure anesthesia is used after reduction. Abdominal viscera are placed in a moist gauze to give more exposure. Small forceps are placed at intervals of $\frac{3}{4}$ inch along anterior border of hernial ring and the broad expanse of renal fascia caught posteriorly. Interrupted mattress sutures of No. 9 silk are placed (Fig. 2) and tied. The viscera are replaced in their normal

position and abdominal incision closed. Air is withdrawn from the pleural space before the child leaves the operating room. Aftercare consists of attention to proper oxygenation and feeding.

Hernia Through Abdominal Wall

Epigastric — According to Luke,²⁷⁸ the great majority of epigastric hernias

2 per cent of 2299 hernias seen at the Royal Victoria Hospital during a 10-year period. Abdominal conditions beside the hernia were found in 16 cases; in 8, a peptic ulcer was associated. At operation on 33 cases, 20 were found to have a sac.

He divides them into 4 groups according to type and symptomatology. (1)

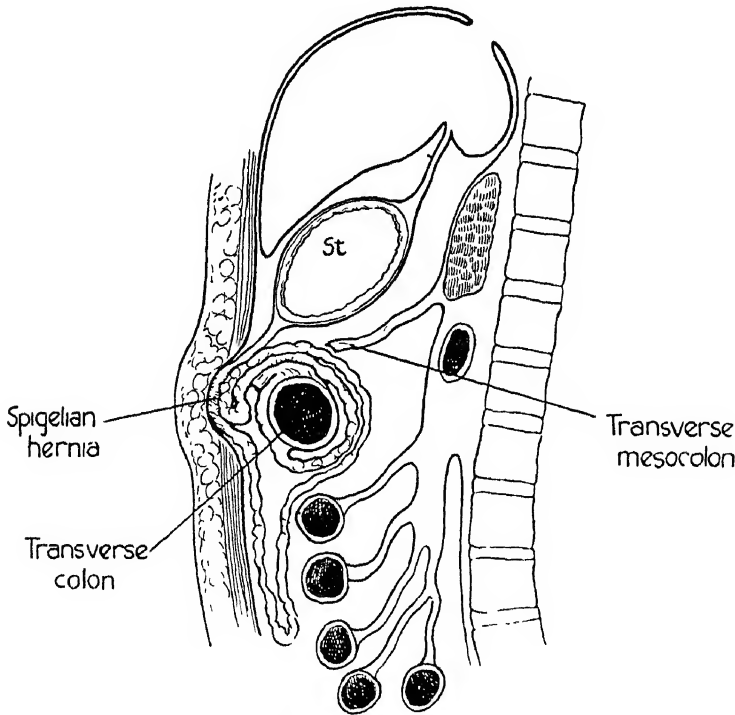


Fig 4—Semidiagrammatic illustration of the mesocolic hernia showing a portion of the omentum passing through the mesocolic opening and pushing into the interior recess of the omental bursa, forcing ahead the anterior wall of this bursa. The relationship of the mesocolic hernia to the spigelian hernia is indicated. (Courtesy, *Am J Surg*, Nov., 1938.)

are acquired and due to strain, which may be acute or chronic. Extended illness and emaciation are predisposing factors. In rare instances, a congenital defect is the causative factor. There are 2 types: The first and most common is a preperitoneal fat mass united to the peritoneum by a pedicle; the second has a true hernial sac.

In 46 cases analyzed, males outnumbered females 42 to 4; the average age was 42.4 years. These cases constitute

Strangulated or incarcerated type with a history coincident with onset of the protrusion. Operation imperative. (2) Type with tender epigastric mass and no visceral complaints. Good results follow the repair and exploration is not necessary. (3) The cases following definite strain or exertion, usually in athletes or laborers. Symptoms disappear with reduction. Good results from simple repair. (4) Those patients with abdominal viscera symptoms, the hernia having been noticed

previously by the patient or discovered for the first time during a physical examination. These cases should have complete diagnostic investigation of the gastrointestinal tract including the gall bladder and pancreas, the renal tract and nervous system. If all tests are negative simple repair may be sufficient, but a combined exploratory and repair is preferred.

That epigastric hernia may be responsible for symptoms of intra-abdominal disease is illustrated by the case reported by Charlton.²⁷⁹ The symptoms and signs of epigastric hernia may be divided into 2 groups: (1) Those local symptoms associated with the hernia, tumor, tenderness at the site of opening, often relieved by recumbency; (2) symptoms of intra-abdominal disease simulating appendicitis, peptic ulcer or gall-bladder disease.

Multiple Hernia—Multiple hernias are not uncommon; however, the combination of an incarcerated umbilical hernia associated with an epigastric, ventral, Spigelian, and mesocolic hernia as reported by Goldberger and Panebianco²⁸⁰ is rather unique (Figs. 3 and 4). A successful repair was accomplished by converting the 4 hernial openings into a single defect and utilizing the Mayo principle of repair.

Spigelian Hernia—Bachy²⁸¹ reports the case of an adult male who suffered from a strangulated hernia through the semilunar line of Spigel. For 12 years he had noticed a mass in the abdominal wall. On the day of operation, he presented signs of intestinal obstruction with a painful swelling in the abdominal wall just external to the rectus abdominus on the left side on a line running from the umbilicus to the left anterior superior iliac spine. At operation the transverse colon and mesentery was found in the hernia. The hernial protrusion was through the aponeurotic

space external to the rectus abdominus along the line of insertion of the transverse and oblique abdominal muscles. He states that this type of hernia is equally distributed between males and females; and usually the patient is between 35 and 40 years with a history of tumor for a long time.

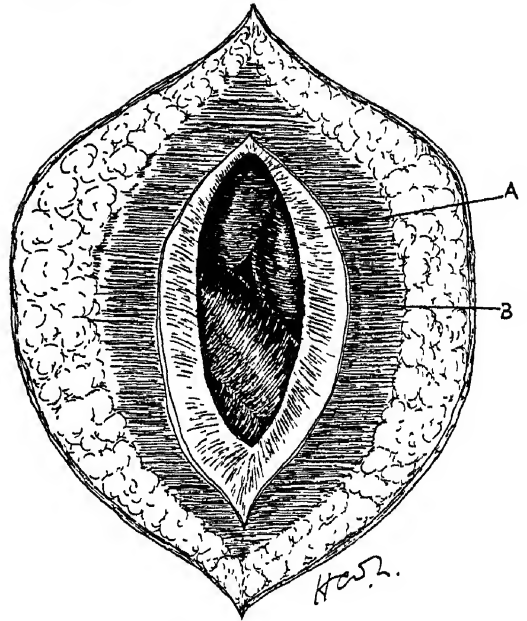


Fig 5—Redundant sac removed, peritoneum ready for suturing, rectus sheath exposed on either side A, Peritoneum, B, rectus sheath (British Journal of Surgery)

Incisional Hernia—A well-known fact that incisional hernia is more common after the paramedian or lower midline incision is emphasized by Coates²⁸². In an analysis of 144 patients operated for incisional hernia the actual mortality from the hernia and its immediate complications was a little over 2 per cent. The advisability of transverse or oblique incisions is stressed as a preventative measure.

Nuttall²⁸³ describes an operation consisting of detaching the abdominal rectus muscles from their insertion at the symphysis pubis, and attaching them in an overlapping manner to the fibrous tissues at the symphysis pubis (Figs. 5, 6,

and 7). Cure was obtained in 2 cases which had been previously considered inoperable. The following principles of muscle transplantation are important: The nerve supply must be preserved intact; the line of action from origin to insertion must be as straight as possible, the muscles should be sutured in moderate tension, muscles should be transplanted into bone if possible, and there

error. Obesity was recorded in 5 per cent of the cases. Ninety-two per cent of the patients had occupations requiring heavy lifting or straining, while only 8 per cent of the recurrences were in patients with sedentary work. The recurrence took place more than 6 months after the operation in 77.5 per cent, and in 52 per cent of the patients there was no recurrence until more than 3 years had elapsed. The

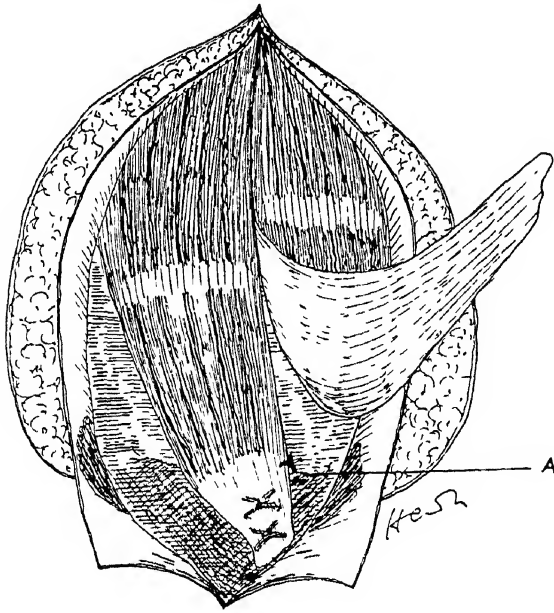


Fig. 6.—Right rectus sutured to opposite side of pubis. A, Upper edge of symphysis pubis. (British Journal of Surgery.)

must be no lateral pull on the belly of the muscle.

Inguinal Hernia — Mortality and Recurrence — Fallis²⁸⁴ analyzed 200 cases of recurrent inguinal hernia with a recurrence rate of 13 per cent, as contrasted to a recurrence rate of 8.25 per cent for primary hernia operations. Ten cases had multiple operations, in 9 the operation was for a second recurrence with 1 recurrence and in 1 instance a successful result attended the fourth attempt at repair. Recurrences were between 30 and 50 years in 78 per cent of the cases. There were 3 females (1.5 per cent) which was considered as a surgical

operation for recurrence was performed within 1 month in 26.5 per cent, and within 1 year in 66.5 per cent. The recurrence was noticed on the left side in 53.5 per cent and the right in 46.5 per cent, which was considered interesting because the right is involved by hernia in the ratio of 3 to 2. The spermatic cord was found to have been transplanted in 20 per cent of this series. There were 99 direct and 101 indirect recurrences, however, an analysis of the 53 patients originally operated at the Ford Hospital showed that 71.7 per cent were of the direct recurrence. As a result of this study, the cord is being transplanted

more frequently. There were 11 sliding hernias. The sac was closed by straight suture in 38.5 per cent; purse string, 30 per cent; twisting, 15 per cent; transfixion, 8.5 per cent, and not opened, 7.5 per cent. The importance of the transversalis fascia was stressed as a cause of direct recurrences. The Bassini type of operation was done in 76.5 per cent with a recurrence rate of 13.7 per cent and the Halstead in 13.5 per cent with a recurrence rate of 10.7. Silk was the suture material in 96 per cent of the cases. There was no mortality. The post-operative complications were pulmonary, 3.5 per cent, hematoma, 1.5 per cent; testicular atrophy, 1.5 per cent; hydrocele, phlebitis and wound infection, each 0.5 per cent.

In an analysis of 1032 patients more than 50 years old, Grace and Johnson²⁸⁵ report a mortality of 3 per cent. The recurrence rate was 25 per cent for primary operations and 34 per cent for recurrent inguinal hernias. These figures, which seem high, were based on anatomical defects while in many cases subjective cure was obtained.

Harbitz²⁸⁶ studied 1046 cases operated for hernia, of these, 836 were non-incarcerated (inguinal, 550—femoral, 47; 108 umbilical, ventral, or epigastric). There was a mortality rate of 0.28 per cent. The incarcerated hernias had a mortality rate of 0.77 per cent.

Operations—Wolfe,²⁸⁷ realizing the importance of complete removal of all the hernial sac, advises certain technical steps to insure it. The usual skin and external oblique aponeurosis incisions are made. The internal oblique and transversalis muscles are separated in the lines of their fibers at a point above the internal ring. The peritoneum is grasped, and liberated downward until the sac has been completely delivered. Care must be exercised in liberation of the prevesical fat

and bladder from the medial position of the sac. The sac is then opened, redundant portion is excised, and peritoneal opening closed with continuous catgut suture. This procedure has removed the bulging peritoneum associated with direct hernia, and also the double sac of the pantaloon or saddlebag hernia. The rest of the repair is completed after the

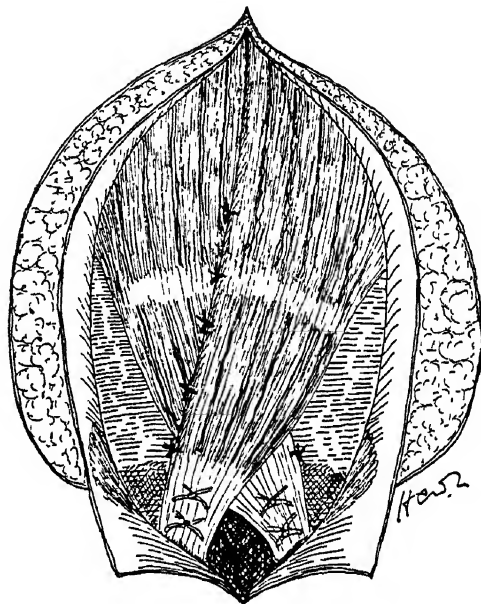


Fig 7—Left rectus overlapping right and sutured to opposite side of pubis (British Journal of Surgery)

Willys-Andrews Method. He treated 41 cases by this method, 21 were followed up with 3 recurrences, of which 2 were repaired by the classical Bassini operation.

In a discussion of the advantages of the abdominal approach to inguinal hernia Williams²⁸⁸ advises a procedure similar to the above except that the technique of LaRoque is followed. This differs in that the peritoneal cavity is immediately opened before the sac is liberated. This approach is particularly advised in cases where the appendix should be removed, in strangulated hernia, in large complicated, indirect hernia, in sliding hernia, in the congenital

type of hernia, and in hernia associated with undescended testicle

The basic importance of the imperfect internal inguinal ring in the production of indirect inguinal hernia is stressed by Benmosche²⁸⁹ To overcome this he devised a method of reconstructing the internal ring with attached flaps

Fleming²⁹⁰ believes that the tissues in the inguinal region are inadequate for repair of hernia in some cases. He considers the transversalis fascia as the first line of defense in repair. Mobilization of the cord is considered necessary for repair of the transversalis fascia, particularly at the internal ring The opera-

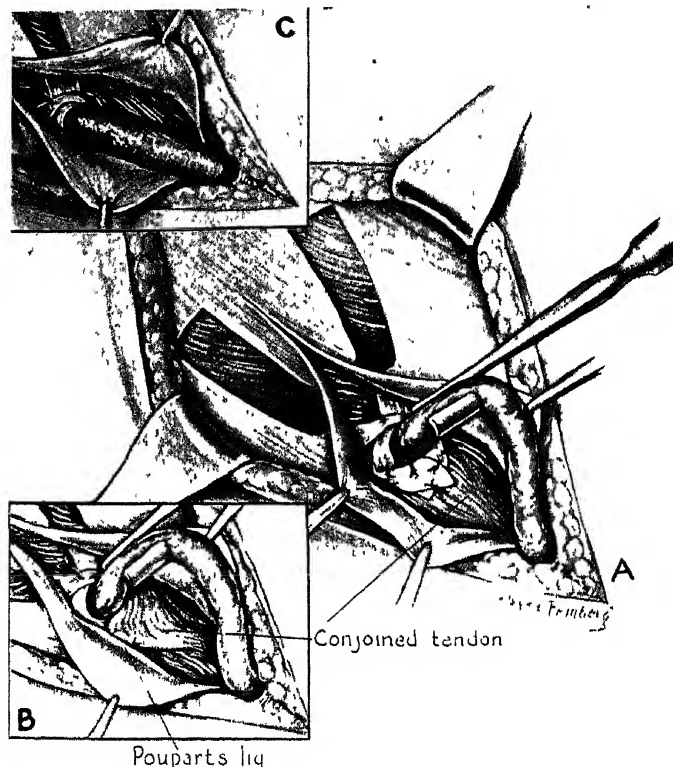


Fig 8, 4—Pedicled flaps around the margin of ring, overlapping at 4 points of circumference B—Upper fibers of conjoined tendon sutured to Poupart's ligament C—Cord placed following reconstruction of ring (Courtesy Am J Surg, June, 1938)

of fascia from the aponeurosis of the external oblique After exposing a wide expanse of the external oblique aponeurosis, 2 pedicle flaps are outlined and the aponeurosis is centrally divided. Exposure, isolation and ligation of the sac as usual. The flaps are then inverted, crossed over each other and tied with a cord retractor in position protecting the cord The pedicle flaps are then sutured around the cord at the internal ring (Fig. 8). The aponeurosis is closed by interrupted sutures.

tion he describes consists of a skin and subcutaneous fat incision curved convexly downward from a point medial and cephalic to the iliac spine ending at the spine of the pubis, which is reflected upward, the aponeurosis of the external oblique is incised ventral to the cord, through the external ring and above the internal ring The sac is isolated, opened, double ones converted into one, closed, and transfixed In operations for direct hernia the sac is opened and transfixed if possible. Transversalis

fascia is sutured so that its edges and the sac are buried. The internal ring is thus closed tightly. A transplant of sufficient size to cover the inguinal floor is removed from the fascia lata of the thigh. Hemostasis secured, the transplant is sutured to the transversalis fascia with continuous 00 chromic catgut. The lateral corners of the flap are sutured above and below the cord. These sutures coapt the transplant with the internal ring. The operation is completed by suturing the conjoined tendon, and internal oblique muscle to the inguinal ligament.

Forty-four hernias were repaired by this method without recurrence except in 4 cases in which the operation failed due to hemorrhage, infection and sloughing of the transplant

Burdick,²⁹¹ *et al*, state that fascia of some kind was used in 1485 operations for hernia; about 70 per cent have been followed from 1 to 12 years. There were 71 nonoperative deaths and 25 operative deaths. Pneumonia was the cause of death in 9 cases. Autogenous fascia was used in 1153 cases, ox fascia in 231, and homologous fascia in 101. Of 133 infected wounds, 92 occurred in cases in which autogenous fascia was used, 13 occurred in cases in which homologous and 28 with ox fascia. A recurrence rate of 29.1 per cent was found in the 975 cases followed up. *Reoperations showed slight evidence of the fascia formerly used.* They also feel that drawing bulky fascia on large needles through the transversalis fascia and Poupart's ligament produces weak spots which predisposes to a recurrence. They have adopted silk technic except for large ventral hernias, in which the pedicled fascial flaps may be used.

Parsons²⁹² found the incidence of recurrence after inguinal hernioplasty with silk technic to be only 3.5 per cent in a

series of 458 cases, as contrasted with a recurrence of 12.7 per cent in a series of 244 cases in which catgut was used. The operative technic as advised by Halsted, and others, involves the slightest possible contamination of the wound, the minimal amount of trauma to the tissues, and the use of the least irritating suture material. Meleney's reports on healing of clean wounds for several years shows a definite advantage of silk over catgut. From these studies it seems reasonable to infer that silk technic rigidly followed is the method of choice for repair of inguinal hernia.

Since introducing alloy steel wire as a suture material in 1932, Babcock²⁹³ has repaired most of the hernias in his clinic with this material. This material has the advantage of being very strong, impermeable, easily sterilized without impairing the strength and produces practically no tissue reaction. Should a wound infection occur the wire will not retain bacteria as the unimpregnated silk. He has for some time opposed the use of fascial sutures chiefly on the basis of their size and the trauma produced by their introduction.

Cavina²⁹⁴ repairs inguinal hernias by Postempski's variation of Bassini's operation, but in order to avoid direct issue of the spermatic cord from the abdomen, he uses the following technic: The muscular layer, with or without the transversalis fascia, is sutured by 3 or 4 catgut sutures to Poupart's ligament. The aponeurosis of the external oblique is then sutured, with catgut, following a direction from the pubic bone toward the anterior superior iliac spine. The spermatic cord is made to leave at a point well above the level of the internal ring, silk sutures are used above and below the opening for the cord. In this manner the cord is forced to make a bend. Kirschner has used the same

method since 1933. The cord is then covered by subcutaneous fat and fascia. Satisfactory results were obtained in more than 1000 cases. The operation is indicated for inguinal laparocele, direct and recurrent inguinal hernia, external oblique hernia with weak and thin abdominal wall, and also with a large spermatic cord which may be injured by the scars left by following Bassini's technic.

The "Bellevue Bridge" has, according to Graham and Coley,²⁹⁵ 2 drawbacks, (1) Being strapped to the thighs it tends to limit motion which is desirable as a prophylactic measure against thrombi and phlebitis, and (2) it is difficult to keep the scrotum in place on top of it, since flexion of the thighs allows the scrotum to slip below the bridge. For this reason they devised a type of scrotal support, which is made from a piece of 12-gauge pliable wire about 32 inches long. The wire is bent in a "V" and the ends shaped in a triangle each side of which is about 1 inch long. An adhesive lap is placed over the lower 4 inches and the free edge is fitted to fit the perineum. The wire shafts and distal triangles are firmly fixed to the bandage above the adhesive. Gauze is placed between the scrotum and bridge.

Direct Inguinal Hernia—Anatomy

--Normally the opening of the external inguinal ligament is protected by the conjoined tendon posteriorly, while in cases of direct hernia the conjoined tendon is usually found weak or absent. Additional factors in producing the weakness are normally large external inguinal rings, the direct insertion of the fibers of the internal oblique in a transverse direction into the rectus sheath, and a deficiency or opening in the transversalis fascia.

Diagnosis—It is important to make a preoperative diagnosis of direct hernia, since the operative technic of repair should be directed toward the defect in Hesselbach's triangle. A weakness or rent in the posterior wall of the inguinal canal is usually made out by careful palpation, and frequently 1 or 2 fingers may be inserted directly into the hernial opening allowing palpation of the rectus muscle medially and the pulsation of the deep epigastric artery laterally. The reappearance of the hernia after adequate pressure made over the internal ring is also helpful. More recently Harris and White²⁹⁶ have found that the length of the inguinal ligament has a direct relationship to the type of hernia. In cases where the inguinal ligament is 15 cm or less, indirect hernia has been found, while an inguinal ligament over 15 cm is always associated with the direct type of hernia.

Operations—From the number of operations devised for the cure of direct hernia we may realize that no one procedure is without failures. In Christopher's Surgery a recurrence rate of 15 to 30 per cent has been found by actual follow-up reports from the leading and best surgical clinics.

The 2 elements that are essential parts of an operation described by Robins²⁹⁷ are fascial suture and the fascial or ligamentous covering of the superior surface of the pubic bone. The use of fascial strips derived from the external oblique aponeurosis was first used by McArthur in 1901. Babcock is credited as being the first to suggest the employment of the fascial covering of the pubic bone in the radical cure of hernia. Briefly the technic may be summarized as (1) Oblique incision with wide exposure of external oblique aponeurosis (2) Opening the external oblique aponeurosis in the direction of the fibers from the ex-

ternal ring by pressure of open scissors (not cutting). (3) Separating 2 aponeurotic flaps on either side starting at the pubic attachment where they are left fixed. (4) Examination for hernial sac, direct or indirect and resection with ligation if necessary. (5) Threading fascial flaps on Gallie needles. (6) Medial flap is passed through the rectus sheath and muscle, over the cord, and takes a firm bite in the fascia that covers the pubic

of external oblique incised along *medial edge of external ring*. (3) Liberation of sac from transversalis fascia and suturing it to the inguinal ligament. (4) Lateral leaflet of external oblique incised at the level of internal ring and sutured to the transversalis under the cord. (5) Upper flap of medial leaflet of the external oblique aponeurosis sutured over the cord to the external surface of the inguinal ligament This

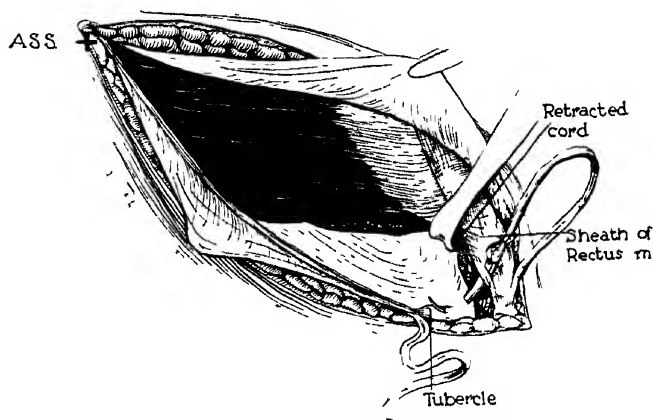


Fig 9—Tissues to be sutured, showing first stitch being introduced. This fascial suture is derived from the medial pillar and is carried through the rectus sheath and muscle and then passes over the cord and takes a firm bite in the fascia covering the pubic bone (Robins Annals of Surgery, Sept., 1938)

bone at the pecten ossis pubis (Fig 9). The fascial stitch is then continued higher upon the rectus and more lateral on the pubic fascia, thence through the internal oblique and transversalis to the shelving portion of Poupart's ligament, the first stitch embracing Gimbernat's ligament. (7) The second fascial suture derived from the lateral pillar is used to unite the aponeurosis of the external oblique. Robbins reports a series of 23 patients with 27 operations of this type without a recurrence in a 3-year period for the longest case. In 14 of the 27 cases a hernial sac was found.

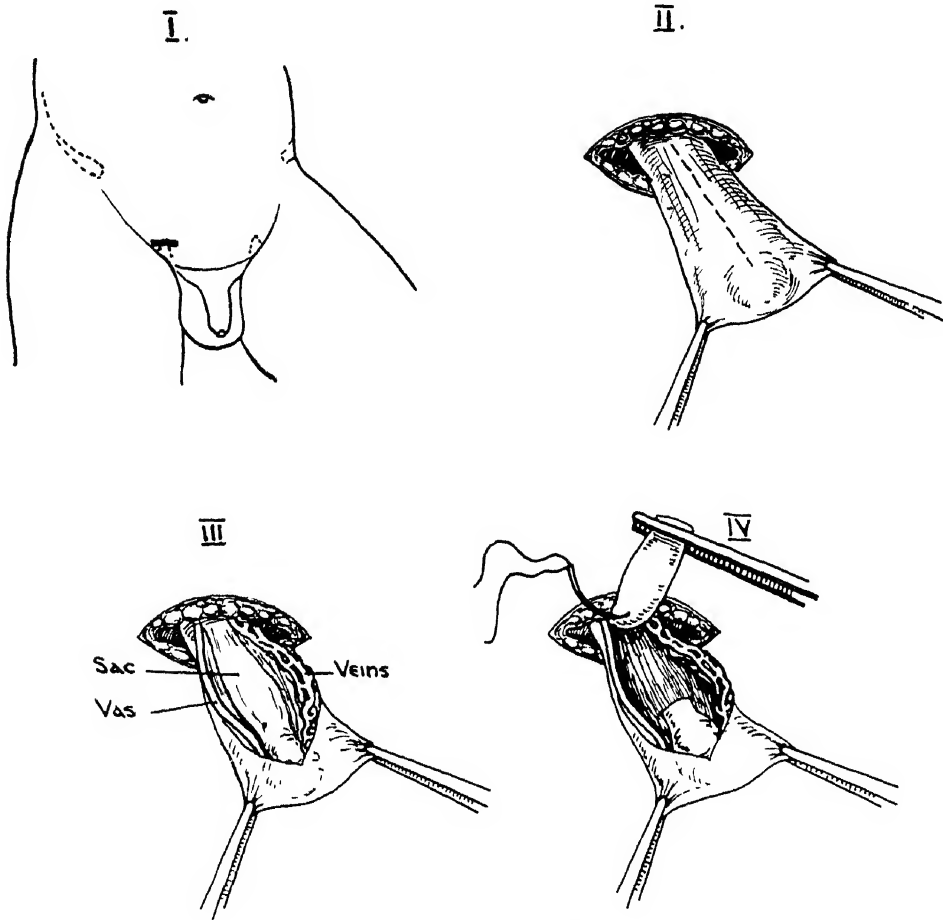
An operation advised by Zimmerman²⁹⁸ may be described as: (1) Usual oblique skin incision. (2) Aponeurosis

method was employed in the repair of 90 direct hernias of which 59 were followed up over a period of at least 1 year. There were 6 recurrences, or an incidence of 10.2 per cent.

Fallis²⁹⁹ exposes the spermatic cord, opens the cremasteric muscle and opens the sac in the manner described by Hogue. The finger is inserted into the peritoneal cavity and the sac of direct hernia pushed up, liberated, and ligated. The medial half of the transversalis is united to Poupart's ligament. The lateral margin of the rectus muscle and sheath, and margin of the internal oblique and transversalis muscle, are sutured to Poupart's ligament under the cord. The lateral flap of external oblique is sutured

to the anterior surface of the internal oblique and rectus muscle. The medial flap is sutured down to Poupart's ligament behind the cord. He reports a recurrence rate of 11.6 per cent in a

have attempted to bridge this defect with a free osteoperiosteal transplant taken from the tibia. An incision 8 to 12 cm. is made over the medial border of the tibia, exposing the anterior surface. A full



HERNIA IN INFANTS

- I Line of incision
- II Cord on stretch Line of incision on Cord indicated
- III Veins and Vas freed off Sac.
- IV Sac isolated and cut after clamping Ligature being applied to neck

Fig 10

(Herzfeld Am J. Surg, Feb, 1938)

series of 154 cases of direct hernia followed over a 2-year period.

Veal and Baker⁸⁰⁰ believe that after the usual methods of repair of a direct inguinal hernia there is still a defect over the pectineal line of the pubis. They

thickness osteoperiosteal graft is removed. The upper portion of the graft is made the size and shape to fit into the defect over the pectineal line of the pubis, this portion contains bone as well as the periosteum of the pubis, with 2

to 4 sutures of 0 chromic catgut. It is then sutured to the posterior surface of the conjoined tendon. The long tail is used as a suture to draw the conjoined tendon down to the inguinal ligament. The conjoined tendon and inguinal ligament are further united by 2 to 4 catgut sutures. The cord is replaced and the external oblique and skin are closed. Skin of the leg is then closed.

They have done this operation on 14 patients since February, 1937. By x-ray they have found that within 3 months the bone becomes absorbed and leaves fibrous scar tissue.

Injection Treatment of Hernia—Fowler³⁰¹ points out that this treatment of hernia should be carried out by a hernial surgeon, who through his operative work has a proper understanding of the anatomy involved. The surgeon must also develop special skill in palpation and "needle feel." It has previously been suggested that a solution of mild dyes be injected to determine the point of injection and diffusion of solution prior to surgical treatment. The importance of careful records of technic, accurate follow-up studies, and extensive research problems have also been pointed out.

The importance of proper selection and supervision of truss pressure cannot be too strongly emphasized as a factor in obtaining good results from this method. This phase has been previously reviewed in detail.^{302, 303}

Solutions—Harris,³⁰⁴ *et al*, have made observations on the following solutions: "A" Piña Mestre Solution; "B" Proliferol; "C" Sylnasol. The criteria used in evaluating them were: (1) Ability of the solution to produce fibrous tissue when injected into experimental animals. (2) Determination of its toxicity when injected intraperitoneally in ani-

mals. (3) The determination of the sterility by bacteriologic methods. (4) Clinical evaluation. They found that the end result of all these was identical from a histologic standpoint, that all solutions used were sterile, that clinical studies showed no advantage of 1 solution over the others, and that all were relatively nontoxic when injected intraperitoneally but that solution "C" Sylnasol was somewhat less toxic.

After experimental work on 6 of the commonly used solutions, Manoil³⁰⁵ drew the following conclusions: The persistence of foreign body giant cells from 2 to 8 weeks after the injection of Galtanol suggests that its clinical use may be unfavorable. The systemic reaction following the injection of Bratrud's solution, and a modification of Mayer's solution, as well as marked necrosis of muscle following the injection of the latter, makes them unsatisfactory. The iodine and tannic acid solution, although producing marked fibrosis in the later stages, should be carefully investigated clinically because abscess formation was noted in the 24-hour sections. Carabba's solution produced mild necrosis of muscle and a foreign body giant cell reaction in 7-day sections, this may be satisfactory for clinical use. Finally, sodium psyllate (Sylnasol) seems to have all the necessary qualifications for a safe and satisfactory sclerosing irritant in the formation of scar tissue. It produces a mild inflammatory reaction, slight necrosis of muscle in the early stages, no systemic reactions when injected intramuscularly, and moderate reaction on intraperitoneal injection. It produces firm scar tissue without any undesirable histologic changes. The advantages of Sylnasol have been previously emphasized.

Evaluation of the Method—Of 573 cases of hernia presenting themselves for

treatment, Harris and White³⁰⁶ treated 236 (41 per cent) by the injection method; 91 (16 per cent) by operation, and 246 (43 per cent) by the application of trusses. Thus it may be seen that 59 per cent of the cases were not suitable for injection therapy for these reasons: The hernia was not reducible in 38 (6.6 per cent); a satisfactory truss could not be fitted in 55 (9.6 per cent), patient preferred operation in 53 (9.4 per cent); treatment not advised because of age or infirmity, 39 (6.8 per cent), patient was satisfied with the truss and refused treatment, 152 (26.6 per cent). Of the 236 cases treated by injection, cures were obtained in 134 (56.8 per cent), possible cures in 66 (27.9 per cent) and known failures in 36 (16.3 per cent). Of the 134 cures, the truss had been removed from 6 months to 1 year in 32 cases, from 1 to 2 years in 62 cases, and from 2 to 3 years in 40 cases.

An analysis of the end results in relation to the type of hernia shows 118 were the pure indirect type with 81.4 per cent cures, 9.3 per cent possible cures, and 9.3 per cent failures; 39 were combined direct and indirect type with 39.1 per cent cures, 48 per cent possible cures and 12.9 per cent failures; 33 were pure direct type with 26.8 per cent cures, 52 per cent possible cures and 21.2 per cent failures; 20 were recurrent postoperative with 21.5 per cent cures, 52 per cent possible cures and 27.5 per cent failures; 5 were umbilical with 100 per cent cures; 3 were femoral with 1 cure and 2 failures; of 9 ventral hernia, 2 were cured, 4 possible cures and 3 failures.

The causes of recurrences and final failures were: Insufficient treatment, 32; improper truss, 3; refusal of patient to co-operate, 8; poor proliferative response, 16; obesity, 6; large size hernia,

2; inability to hold hernia with truss due to pain, 1; due to cough, 2; due to unknown cause, 5; sliding hernia, 2; discontinuance of treatment due to dermatitis from truss pad, 2. Of the final failures, 14 had hernias one-fourth to one-half the previous size and were easily held with truss, 11 had a hernioplasty, and 11 more were to have operation. The authors state that the operative work, while technically more difficult, has convinced them that binding adhesions between muscle and fascia are produced by the use of chemical irritants.

In this series of cases there were no deaths and no serious complications which required hospitalization. Complications such as transient swelling of the cord, hydrocele of the cord, epididymitis, transient shock due to intraperitoneal injection and dermatitis were of minor consequence.

The conclusions are that the end results are not comparable to those of operation, however, they are sufficiently good to recommend this treatment when operation cannot be considered for economic, personal or physical reasons. This method of treatment if the object is cured should be limited to a small group of subjects whose inguinal ligaments measure about 13 cm. The field of usefulness can be extended if the object is possible cure with continued truss wearing.

That injections of hernia may carry a certain risk to life is emphasized by the report of 2 fatal cases reported by Berne.³⁰⁷ In both cases death was caused by a perforation of the bowel, secondary to intraperitoneal injection of the sclerosing agent. In 1 instance quinine and urea hydrochloride was used, in the other case the sclerosing agent was unknown. In 1 case the acute process progressed from the time of injection and was operated 3 days later, in the other after

an initial syndrome suggesting severe irritation of the bowel wall a quiescent period occurred with a sudden progressive episode 5 days later. It is advised that laparotomy may be necessary at any time, as an emergency procedure, on the appearance of symptoms and signs indicating a significant variation from the usual clinical course following intraperitoneal injection.

Hernia in Infancy and Childhood

—Inguinal hernia is by far the most common form, and usually makes its appearance in the early weeks of life. It occurs in males and females in the ratio of 9 to 1, according to Herzfeld³⁰⁸. The complete or total funicular type is rare and in a series of 1000 consecutive cases it accounted for only 5 per cent. The partial funicular hernia accounted for 95 per cent. It is important to determine if the hernia is reducible, irreducible, obstructed or strangulated. In the male, small intestines are usually in the sac; however, the cecum and appendix may be present (sliding type), while in the female the ovary is commonly found.

The treatment of inguinal hernia in infancy may be neglected, active conservative (truss) or operative. An infant under 6 months may be treated by an inflatable truss with pelvic band and perineal pad, while in older babies a celluloid spring truss may be applied. The truss should be worn continuously day and night for 3 to 6 months. This has the disadvantage of being difficult to maintain, care must be exercised to prevent skin excoriation and an apparent cure may not be permanent. The operative treatment as outlined by Herzfeld is very fascinating; any healthy child 4 weeks or over is eligible for operation, and it is considered advisable to get the operation over before teething or walking occurs. The infant is not

kept in the hospital more than 2 or 3 hours after the operation. Ethylchloride and open ether are the anesthetics used. The operation consists of a small transverse skin incision over the external abdominal ring, picking up the cord and delivering the testicle, *using 2 fine artery clamps the cord is put on the stretch, so the anterolateral aspect presents*, the 3 coverings of the cord are divided in a line parallel with the line of the veins, the sac is located and with blunt dissecting forceps the coverings are stripped off in a transverse and circular direction. Having freed the sac the fundus is clamped and divided immediately distal to the forceps, the fundus is examined to ascertain the type of sac and then dropped back into the scrotum, the proximal portion is carefully isolated by dissection and pulled down until the extraperitoneal bladder fat appears on the inner side, the sac is then transfixed with No. 1 chromic catgut, excess sac cut off, 1 stitch across the region of the pillars of the ring, skin closed with 1 or 2 Michel clips. A small piece of gauze is applied to the wound, over which is affixed an oval piece of sterilized adhesive about 4 inches in its longest diameter. Sutures or clips removed on fourth day after operation.

The rare *congenital umbilical hernia* (exomphalos) is described by Herzfeld, for which immediate operation is advised. For the small postnatal umbilical hernia conservative may be tried for 2 to 6 months. For cases with a hernial opening less than $\frac{1}{2}$ inch subcutaneous ligation, a minor procedure is advised. Three radiating incisions $\frac{1}{2}$ inch are made close to the umbilical scar; each is deepened to the aponeurosis, with fine artery forceps; tunnels are made between each incision just superficial to the aponeurosis, a strong ligature of 20-day catgut encircles the sac, and after reduc-

ing the contents the ligature is tied. Pressure pads are used for 1 month. In the larger umbilical hernia, the hernial sac is isolated and ligated through a small curved incision around the umbilicus, the edges of the gap in the aponeurosis are approximated with 2 or 3 interrupted catgut sutures.

In a series of 1000 cases of hernia in children up to 12 years Herzfeld found only 4 cases of femoral hernia, 3 females and 1 male. Where operation is required, exposure and ligation of the sac through the inguinal canal is recommended.

Incarcerated Hernia — Thorndike and Ferguson³⁰⁹ report a series of 106 children under 12 years with incarcerated hernia; of these true strangulation occurred in only 5 cases, during the same 10 years 1740 operations for inguinal hernia were performed. The ratio of incarceration to the number of hernia is 1 to 17. The greatest incidence of incarceration occurred during the first 6 months and after the age of 18 months there was a steady fall to the age of 6. Males were affected in 96.2 per cent of the cases and females in 3.8 per cent. The right side was involved in 80.2 per cent, against 19.8 per cent on the left. There was a mortality of 2.83 per cent. Of the 3 fatal cases, 1 died without operation, at autopsy an incarcerated right inguinal hernia containing the cecum, appendix, and terminal ileum, with acute obstruction and an advanced stenosis of pylorus, another died 8 hours after operation, probably as a result of acute obstruction; the third was operated after unsuccessful attempt at reduction for 5 hours, there was grayish yellow fluid in the sac which cultured out *B. coli*, the testicle was gangrenous. At autopsy a perforation of the terminal ileum was found.

The authors believe that in the absence of obstructive symptoms, conservative

measures for reduction should be attempted for 3 to 5 hours before resorting to operation. They were able to reduce 75 per cent of the cases in the past 4 years by conservative measures. If reduction is effected the hernia should be held by a yarn truss for 48 hours or until the edema subsides. Then operative repair performed. They follow the Ferguson technic and feel that all cases should have the inguinal canal opened and repaired. The sutures are of black silk.

Acute Hernial Appendicitis—Since acute inflammations of the appendix associated with right inguinal hernia is more prone to occur in infants and the very old it seems logical to consider it at this point. Burger and Torbert³¹⁰ in a series of 449 cases of acute appendicitis found the appendix in a right hernial sac in 3 cases (0.67 per cent). They report the case of a male infant born 2 months prematurely who was operated upon at 6 weeks of age. At operation a gangrenous appendix was found in the hernial sac, there was no constriction at the internal ring. The infant died on the second postoperative day. Helpful points in the diagnosis are: The ability to outline the appendix in the hernial sac, the presence of a small, firm, tender area in the supposedly strangulated hernia, right abdominal tenderness and rigidity; intermittent pain, sudden cessation of pain (perforation), fluctuation in the hernial mass.

Femoral Hernia

Usually the sac of a femoral hernia contains omentum, less frequently intestines or bladder, however, recent reports are made of an ovary and a Meckel's diverticulum being found.

Bowen³¹¹ reports the case of a woman 38 years who complained of severe pain in the femoral region for 11 days.

She first noticed a right-sided femoral lump 10 years before. At operation the right ovary was found in a femoral hernia, resection and repair were followed by cure. He was able to gather 23 other cases from the literature. Atrophy, cystic, inflammatory changes, and malignant changes may develop in an ovary in a femoral hernia. The diagnosis is made at operation, however, an irreducible mass in the femoral or inguinal region in a woman should lead one to suspect herniation of the internal genitalia. Displacement of the uterus toward the affected side with a cervix pointing in the opposite direction may help in making the diagnosis. The *treatment* should be **reduction** or **resection** with hernial repair.

An unusual strangulated Littre's femoral hernia with spontaneous fecal fistula has been reported by Weinstein.³¹² He analyzed 32 cases in which a Meckel's diverticulum was found in a strangulated or incarcerated femoral hernia; of these 24 were considered to be strangulated. In 6 of the 24 cases a spontaneous fecal fistula occurred; 1 died. In 4 instances in which there was a perforation into but not through the sac 3 patients died.

Littre's rules as transcribed by Mason: "The diagnostic signs making this type of hernia recognizable before operation are:

"1. The patient goes to stool during the whole course of the illness as, the intestinal canal being uninterrupted, the excrements are at perfect liberty to pass from one end to the other.

"2. The patient has no hiccough, or very occasionally

"3. He does not vomit, at least by comparison less frequently than in ordinary hernia. The vomitus is never fecal

"4. The patient's belly is never fat, stretched or full of wind as in ordinary hernia

"5. The tumor in the groin is formed more slowly and never becomes larger.

"6. The inflammation, fever, pain or other symptoms which may accompany this particular kind of hernia are less severe and take longer to manifest themselves than in other herniae.

"The diagnostic signs which make this particular hernia recognizable during operation are:

"1. In ordinary cases of hernia, the entire circumference of the intestinal body is engaged in the hernial sac, this hernia there is only 1 part in the sac.

"2. The portion of the intestine which forms an ordinary hernia is found doubled in the shape of an arc in the sac. In this particular kind (which concerns us) this portion is single, situated perpendicularly and terminated by a very distinct end

"3. An ordinary hernia is often formed by intestine and omentum together. This particular kind is always made by intestine alone"

Treatment — Burrows,³¹³ realizing that the percentage of recurrence is too high for femoral herniorrhaphy, advises a return to the simple technic as advocated by Ochsner. This consists of simple incision over the femoral sac, liberation of the sac being careful that it is nowhere adherent to the femoral ring, reduction of the contents by division of adherent viscera if necessary, high ligation of the sac allowing it to retract into the abdomen, and closure of the skin. The femoral ring is not closed. He has heard A. J. Ochsner say, "When the circular femoral ring is closed with plain catgut, the percentage of recurrences is small. When the orifice is sutured with chromic catgut the percentage of recurrences is greater. When silk is used, the recurrences are still more numerous. When the femoral ring is distorted by an attempt at closure with silver wire, most of the operations fail." For strangulated femoral hernia it may be necessary to cut the femoral ring medially. This should be repaired by restoring the femoral ring to a circular opening, without an attempt to ob-

literate the ring. For the large femoral defects the method of Edmund Andrews is advocated. If the conjoined tendon is developed it is sutured to the pubis, in its absence the defect is repaired by a turned-in flap from the external oblique aponeurosis.

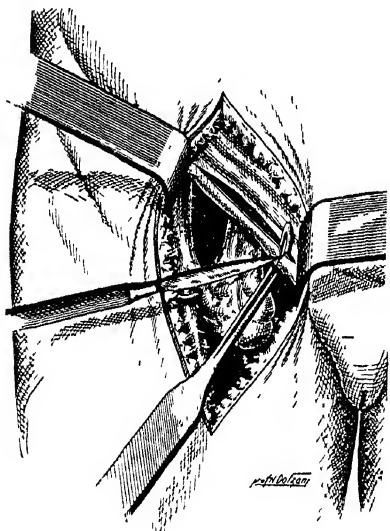


Fig. 11—Resection of the inguinal ligament near its pubic insertion. (Clin. Chir., 1937.)

A new technique of femoral herniorrhaphy is presented by Frassmetti.³¹⁴ Careful dissection of the inguinal ligament allows easy access and manipulation of the deeper strictures (Fig. 11). This is valuable in strangulated hernia, since it gives enough exposure to allow reduction without undue trauma or to do a bowel resection. The sac is isolated and opened, contents reduced or resected. Redundant sac is removed and ligation high enough to obliterate any bulge of the peritoneum (Fig. 12). The structures making up the inguinal ring should be carefully identified and dissected out especially posterolaterally, in order to expose Cooper's ligament and the large femoral vessels. The hernial orifice is closed by sutures taken through the internal oblique, transversalis fascia, and Cooper's ligament, including also

the anterosuperior border of the sectioned inguinal ligament (Fig. 13). The aponeurosis of the external oblique muscle is now lowered and the cord or round ligament replaced in its original position. The aponeurosis of the external oblique muscle is sutured to Cooper's ligament and in this position the overlying inguinal canal is reinforced. He operated on 23 patients in 5 of whom the hernia was strangulated. In 1 a gangrenous loop of bowel had to be resected. No recurrences were noted.

Intra-abdominal Hernia

Intra-abdominal hernia is a term used to include the various types of internal hernia, *i. e.*, the duodenal hernia, the right and left paraduodenal hernia, hernia into the ascending mesocolon or mesentericoparietal hernia. Alexander

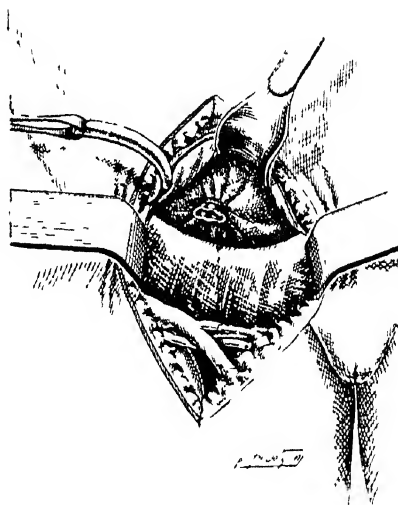


Fig. 12—Ligation and section of the hernial sac and replacement of the stump into the cavity. (Clin. Chir., 1937.)

³¹⁵ has reported 5 cases of this type from the clinical and roentgenologic aspects. The roentgen diagnosis is made by frequent observations of the barium meal as it passes through the small intestine, noting distention, fluid levels, encapsulation of loops of small bowel,

and little or no change in position of the small bowel by pressure or change of posture. Clinical suspicion is aroused by abdominal pain which is exaggerated by exercise, the erect posture and eating bulky meals; but relieved by recumbency, and frequent small feedings with low roughage foods.

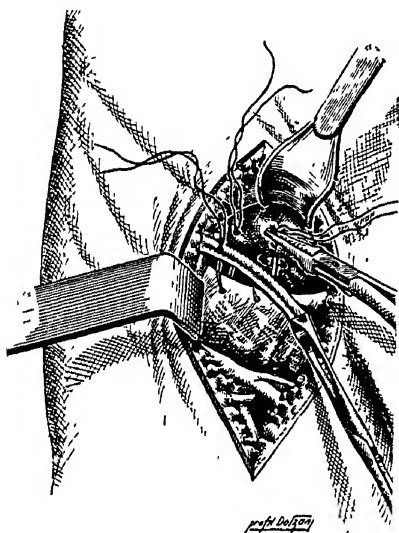


Fig. 13—First step in the closure of the hernial orifice (Cln. Chir., 1937)

Right Paraduodenal Hernia.—According to Baumeister and Hanchett³¹⁶ there have been 44 cases of this type of hernia reported in the literature, this has not included the case reported by Paul and Hill. Nagel in 1923 collected over 100 cases of the left duodenal type of hernia. The case reported by Paul and Hill³¹⁷ occurred in a female baby of 3 months who died of obstruction soon after admission. Baumeister and Hanchett's case occurred in a girl 21 years who was cured by operation. The case reported by Averbach³¹⁸ occurred in a boy 14 years who had sudden abdominal pain followed by nausea and vomiting; operation resulted in cure of the condition.

The right paraduodenal hernia may be differentiated from the left paraduodenal

hernia by observing: (1) The opening of the sac, in the right type the opening of the sac is on the left side and faces left, while in the left type the opening of the sac is on the right side and faces right. (2) The relation of the vessels to the sac, in the right type the superior mesenteric artery runs in the neck of the sac anteriorly, while in the left type the inferior mesenteric vein runs in the neck of the sac anteriorly.

Transmesenteric Hernia.—According to Iagnov and Timus³¹⁹ 55 cases of transmesenteric hernia have been reported, this includes 2 of their cases. The most frequent site of these hernias is at the level of the root of the mesentery near the ileocecal junction. The next greatest number are situated at the center of the mesentery, and the least number at the intestinal border. The gaps in the mesentery may be congenital, traumatic or inflammatory. The congenital type are the most frequent, occurring in 48 of the 55 cases. Trauma producing mesenteric lacerations with subsequent absorption of the mesentery was thought to be the cause of 5 cases.

In an analysis of 342 cases of acute intestinal obstruction occurring in Japan, Tadyo³²⁰ found that internal hernia caused 4 cases. Of these 1 was of the transmesocolic type without a sac proper, occurring in a 74-year-old man who recovered following operation.

Posterior Vaginal Hernia

True posterior vaginal hernia is a rare type of hernia. Black³²¹ states that only 67 cases have been recorded including the 2 cases he reports. The primary etiologic factor is a posterior congenital defect, an imperfect or complete lack of fusion between the rectum and vagina, in addition to a congenital low peritoneum with a weak pelvic floor. The straining at labor or defecation and in-

creased intra-abdominal pressure due to tumor or fluid are additional factors. The point of descent is usually through the median line of the pelvis which is the weakest. The hernial ring is generally formed between the uterus anteriorly, the rectosigmoid posteriorly and the sacrouterine ligaments laterally. This condition should be differentiated from vaginal cysts, tumors, cystocele and rectocele. Cysts and tumors do not increase in size on coughing, straining nor do they empty on pressure. On rectal examination a rectocele does not enter the protruding mass. A gurgling sound is present when intestines fill the sac, while omentum has a soft mass. Complications attending posterior vaginal hernia, as reported by Bueermann, are: (1) Interference with normal delivery, 0 cases; (2) hernia incised or excised due to error in diagnosis, with death, 3 cases; (3) pelvic abscess following delivery with spontaneous recovery, 2 cases; (4) rupture of hernia with recovery, 1 case; (5) death from incarceration of vaginal hernia, 1 case. The treatment is surgical; with small openings and sacs simple ligation of neck of sac with transfixation to the posterior uterine surface, or the vaginal vaults, celiotomy with correction of pelvic pathology and closure of the sac internally for large hernia, and hernia associated with injury or obstruction of the intestine.

Mediastinal Hernia

A mediastinal hernia is a projection through the mediastinum of 1 pleural space into the other hemithorax. Ellison³²² has reviewed the origin and mechanism of production of these hernia. Artificial pneumothorax is the most common cause, although spontaneous pneumothorax may be the cause. There are 2 "weak spots" in the mediastinum, 1 between the sternum and the front of

the heart at the site of the atrophied thymus; the second further below and posteriorly, and is bounded below by the curvature of the diaphragm. The mechanism by which these hernias are produced is either an excessive pressure in 1 pleural space or a negative pressure in 1 and normal in the other; then instead of the entire mediastinum shifting the weak spot gives away.

Hernia and the Law

The workmen's compensation act provides in part: An employe in order to be entitled to compensation for hernia must clearly prove that its appearance was accompanied by pain; that it was immediately preceded by some accidental strain suffered in the course of the employment. In the case of Hallack & Howard Lumber Co. vs. Bagley (Colo.) the court ruled that outward evidences of an injury need not become immediately apparent,³²³ it is sufficient if it becomes apparent in a reasonable time.

In the case Continental Baking Co. vs. Industrial Commission (Utah)³²⁴ the Supreme Court held that The word "accident" is not limited to any arbitrary legal, technical, or contractual meaning. The injury is an "accident" when it results, not from wear and tear on the body of the workman, but when it occurs unexpectedly as a result of work being done. To render an injury accidental does not require that the strain be such that men would not attempt it or would anticipate probable injury therefrom. It simply means that the effort exerted, considering the position in which the workman was put by the work being done at the instant of the injury, was such that an injury resulted.

Compensation—The injection method of treatment is not authorized and will not be paid for in W. P. A. and federal

employee cases. Fowler³²⁵ feels that this will be taken as official government condemnation of a mode of treatment, which, if followed, as a precedent, is likely to hamper progress on more than this 1 medical front. He has treated 19 cases, working for the government, who paid for the treatments themselves, and after successful cures have been passed by government examiners as cured and eligible for promotion. The private compensation carrier takes a more liberal and considerate attitude.

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ANESTHESIA

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INHALATION ANESTHESIA

The Airway in Inhalation Anesthesia—The knowledge of the proper maintenance of an efficient airway at all times during general anesthesia is probably the most important fundamental of anesthesia. This knowledge of the airway should include the conditions which may be present before operation which contribute toward an impaired airway as well as those conditions which are likely to supervene during the anesthetic period. The immediate effects of an inefficient airway are predominantly upon respiratory function. There is a decrease in the amount of oxygen inspired by the patient, as well as an interference with the elimination of carbon dioxide. The improper expansion of the lung will entail secondary effects upon the circulation. Convalescent respiratory complications are increased when an inefficient airway is allowed to be present, especially the incidence of pulmonary congestion. If the intake of oxygen is too greatly interfered with, the presence of anoxia and anoxemia will develop.

An excellent contribution in this respect by Camel¹ is quoted. "Pathologic conditions that might be present prior to anesthesia that might lead to obstruction to the airway during (the period of maintenance of) anesthesia are: Polypoid growths or other tumors of the nasopharynx, hypertrophied turbinates, deviated septums, large adenoids and tonsils, hay fever, peritonsillar abscess, paralysis of a vocal cord; edema of the glottis; infections with swelling, foreign bodies, aneurisms, cellulitis, enlarged lymph nodes pressing against the larynx or trachea, large or retrosternal goiters; scars; infections in, or tumors of, the

mediastinum; tumors of the tongue; ankylosis of the jaw, and tumors of the larynx.

"Among those that come during anesthesia, either in normal cases, or in abnormal ones like those mentioned, are: Falling back of the tongue, obstructing the pharynx, rigid jaw associated with the above, glottic or laryngeal spasm, falling down of the epiglottis, closing off the glottic opening, blood or mucus or stomach contents, loose dentures, foreign bodies, incidental to the operation, like pieces of tumor, adenoid, tonsil or teeth, misplaced forceps hanging across the trachea, a foreign body in the form of an improperly restrained nasal airway, put in by the anesthetist to relieve obstruction, that slips into the trachea.

"Obstructions due to diseased conditions and deformities are best taken care of when the condition is diagnosed ahead of time, and adequate preparation made to take care of it. Marked nasal obstructions are circumvented by propping the mouth open before induction to prevent locking of the jaw in the early stage. As soon as the (reflexes of) pharynx will permit, insert an oropharyngeal airway. Trouble from large adenoids and tonsil can largely be avoided if sufficient basal (narcosis) is given to avoid excitement (there is instituted a) gas induction with sufficient oxygen to avoid cyanosis, and the slow addition of ether if it is used. Endotracheal maintenance through a Magill tube is very satisfactory to the operator after he accustoms himself to the presence of the tube. Where obstruction is due to pressure on the larynx or trachea from enlarged lymph nodes, new growths, thyroids or aneurisms, the introduction of an endotracheal tube as

soon as possible relieves or prevents trouble. For plastic work on the nose or its floor, lips, eyes, or any other part of the face or mouth, endotracheal maintenance gets the anesthetist out of the way, assures an excellent airway, and permits the movement of the patient's head by the surgeon at will. The same is true of (anesthesia for) brain surgery. This is especially important where the face is covered, and, should any obstruction develop, it would be hard to work without soiling or misplacing the sterile drapes, or interrupting the surgeon in his work. In upper abdominal surgery, endotracheal maintenance is quite helpful, for it not only prevents an obstructed airway and helps to make the proper stage of anesthesia easy to maintain, but it makes it possible for the anesthetist to stop the patient's respiration while a difficult piece of work is being done by the surgeon; work on the common duct for instance.

"One of the most troublesome complications to be dealt with during anesthesia is laryngeal spasm. If it is only partial, a crowing respiration being evident, sometimes a steady pressure on the breathing bag will overcome it and permit the stage of anesthesia to be deepened to the point where it will not recur. An endotracheal tube is wished for, but its passage is not practical because the opening through which it should go is closed. The exposure of the larynx with the laryngoscope and a tube ready to insert at the first sign of relaxation will make its passage possible. The only 100 per cent satisfactory dealing to have with spasms is to prevent them."

Helium

Since this gas is inert, its value depends on its low specific gravity and property of rapid diffusion. A mixture of 80 per cent helium and 20 per cent

oxygen is about one-third as heavy as air and slightly less than one-third as heavy as pure oxygen. Due to its low specific gravity, the rate of flow of this gas through a narrow orifice conforms to the law that the flow of any gas through narrow orifices is proportional to the square root of the molecular weight of the gas. In other words, the addition of this gas to any gaseous mixture "thins out" the resulting mixture. This "thinning out" allows the resulting mixture to be moved with less effort and also to pass through small spaces at a greater flow. Helium is now supplied by manufacturers in cylinders which may be attached to the ordinary gas machine. Because of its expense it is rarely employed except during the use of the carbon dioxide absorption technic. Eversole² gives us the following technic for the administration of helium when the respiratory obstruction is present before anesthesia: "A flow of approximately 3 liters of helium and 1 liter of oxygen is started and the mask is immediately placed on the patient's face. The patient is allowed to breathe this mixture for from 5 to 10 minutes or until the obstruction is relieved. The bag is emptied each time it becomes distended. The flow of helium is then discontinued, the flow of oxygen is decreased to the estimated requirement of the patient and cyclopropane is added, usually at the rate of from 300 to 500 cc per minute, until the patient is anesthetized. If it is necessary to add more helium, the same method is employed as that to be described for the administration of helium to patients in whom an obstruction has developed after they are anesthetized."

Helium is occasionally indicated during the course of an anesthetic when a respiratory obstruction develops. This is especially true when it is felt that it is not indicated to intubate the patient as

for a very short procedure, or it is made use of during the period necessary to establish a plane of anesthesia of sufficient depth to carry out the technic of intubation. In such a situation, the administration of helium is managed by allowing the breathing bag to become filled with a mixture containing (a) sufficient of the anesthetic to maintain the required level, (b) sufficient oxygen to maintain metabolism, and the remainder of the mixture being helium. It should be emphasized that the addition of helium should not be carried to the extent that oxygen deprivation supervenes.

Eversole in giving us the results in 110 cases reports 87.6 per cent of the patients obtained either complete or partial relief of obstruction by the administration of helium, but 12.4 per cent did not obtain any relief. He also has employed helium "a few times as an aid to breathing for patients with partial respiratory paralysis caused by spinal anesthesia."

Sykes and Lawrence³ experimented on themselves and found that an artificial atmosphere of helium and oxygen is theoretically and practically about twice as easy to breathe as ordinary air. When obstruction is present, its value in reducing the amount of work done by the patient and in preventing postoperative collapse of the lung because of its low solubility.

A Reflex Complicating Anesthesia During Abdominal Surgery

Burstein and Rovenstine⁴ have described for us a condition which anesthesiologists have occasionally observed for many years. This is the appearance of abdominal rigidity coincident with a marked diminution of the pulse pressure (even to the point of an inability to obtain a blood pressure reading) during surgical procedures in the upper abdo-

men. Following a discussion of examples of vagosympathetic reactions resulting from direct nervous stimulation, the effect of preanesthetic medication on the sympathetic or parasympathetic nervous system and the exaggeration of autonomic reflexes due to anesthetic agents, a new reflex is described as observed by the authors, during the clinical application of inhalation anesthesia. Their experimental work is also quoted:

"Factors which seem to intensify a disturbance resulting from manipulation of viscera in the neighborhood of the celiac ganglion are. The placing of a sandbag under the lumbar region of the patient, breaking the table so as to extend the epigastric region, excessive pressure upon deep retractors, and the use of numerous packs in the abdomen."

This diminution of pulse pressure in an unimpaired patient may not be of great importance, but in a weak and hyporesistant patient this reaction in blood pressure may prove to be more serious and even fatal.

They believe that this reaction occurs in sympathotomic patients, and it might be prevented if this state of sympathetic hyperactivity could be discerned preoperatively. For this they recommend 2 tests. The first of these is the oculocardiac reflex. When pressure on the eyeball results in bradycardia, the subject is said to be vagotomic. When the oculocardiac reflex shows an increase in pulse rate, it denotes sympathotomia and subjects with such a reaction are difficult to anesthetize. The second test which is designed to study the reaction of the autonomic nervous system by way of the celiac plexus is the oscillometric method of Laignel-Lavantine. This test registers variations in oscillations upon manual pressure in the region midway between the umbilicus and right costal margin. The celiac plexus reflex is said to be

positive and indicative of sympathotonia when a definite diminution in amplitude of the oscillation occurs. In 1 case report described, the oscillations decreased from 5 to $1\frac{1}{2}$ when manual pressure was exerted in the celiac region and immediately returned to 5 when the pressure was released.

The authors summarize as follows: "Observations have been presented which show that disturbances of a reflex nature, characterized by abdominal rigidity and a marked reduction of the pulse pressure may be caused by visceral manipulation during surgical intervention in the upper abdomen.

"This reflex has been produced experimentally in the dog by compression of the celiac ganglion and is particularly evident when there is a vagal paralysis and sympathetic stimulation, whereas parasympathetic stimulation prevents and corrects it.

"Clinically, as shown by case reports, the reflex is observed during upper abdominal surgery in patients with a hyperactive sympathetic nervous system who are premedicated with atropine and anesthetized with ether

"When such patients reveal an active celiac plexus reflex in the preoperative examination, it is suggested that physostigmine be considered for premedication and that the anesthetic agent selected be one which does not stimulate the sympathetic (Ether and chloroform avoided) When this reflex occurs during operation, it is recommended that visceral manipulation be curtailed as much as possible and if this is insufficient the administration of physostigmine may be beneficial "

Cyclopropane

This anesthetic agent has shown a constant increase in use, apparently, throughout the entire country Reports follow-

ing its careful application show it to be a very satisfactory anesthetic gas. Some experimental work has been done in the past year including that of Burstein,⁵ who reports on the effect of cyclopropane on intestinal activity *in vivo*. He has shown that only beginning in the lower planes of the third stage are the contractions of the intestines inhibited, but that their tone is maintained. In the upper 2 planes of the third stage of surgical anesthesia, in which the majority of surgery is performed, cyclopropane causes an increase of both intestinal contraction and tone. This is in contradistinction to ether, which causes an abolition of the contraction in all planes of surgical anesthesia. Robbins and Baxter⁶ have shown that it is only in deep anesthesia that cardiac output is decreased in dogs. This decrease in the output present under deep anesthesia rapidly returns to normal or to an increase in output when the higher planes of anesthesia were re-established.

The clinical use of cyclopropane is nicely summed up in an article by Eversole, Sise and Woodbridge:⁷

"The combination of quiet respiration, ease of induction, and potency, together with an adequate oxygen supply makes this anesthetic suitable in almost any situation in which an inhalation anesthetic is desired These factors combined with a relatively low toxicity leave very few contraindications to its use. Its advantages are most outstanding under the following conditions:

"1 **Situations in Which Excess Oxygen is of Value**—(a) **Thoracic Surgery**—The increased oxygen in these cases is frequently of great benefit since many of these patients are in a rather markedly debilitated state and, in addition, usually have damaged lung tissue with consequent decrease in absorptive surface. These conditions combined with a position on the operating table in

which respiratory excursion is greatly limited make the maintenance of anesthesia without anoxemia with the less potent drugs such as nitrous oxide and ethylene very difficult, and in some instances practically impossible.

"(b) **Hyperthyroidism**—The increased metabolic rate of these patients makes quite obvious the advantage of an anesthetic agent which insures an abundant oxygen supply at all times.

"(c) **Respiratory Obstruction**—In any case in which the adequate exchange of gases is impaired by any type of respiratory obstruction, an anesthetic which is sufficiently potent to be efficacious in low concentration and at the same time carry with it a large supply of oxygen is of very great value.

"(d) **Cardiac Disease**—The use of cyclopropane in the presence of a serious cardiac lesion is certainly debatable in view of our present knowledge of its effect on the circulatory system. We feel it is the anesthetic of choice for these cases; it deep anesthesia (third plane) is not required for the surgical procedure anticipated. However, the circulation should be watched very closely in these cases, and any change such as a drop in blood pressure, the development of an arrhythmia not present before the anesthesia or any considerable change in pulse rate should be a signal for immediate lightening of the anesthesia by the addition of oxygen.

"(e) **Anemias**—In patients suffering from anemia with the consequent decreased oxygen carrying capacity of the blood, the value of an anesthetic agent of such strength that increased oxygen supply is possible, becomes quite evident.

"(f) **Debility and Shock**—Before the advent of cyclopropane we ordinarily used local anesthesia on patients markedly weakened by shock or other causes, because we felt that the admin-

istration of the general anesthetics then available, put too much of a burden on them. Now, however, we feel that we can safely give them cyclopropane because of its low toxicity and because of the high beneficial concentrations of oxygen that may be used with it. Moreover, this adds to the comfort of the patient, and facilitates the work of the surgeon.

"2 **Intratracheal**—The complete abduction of the vocal cords which cyclopropane anesthesia usually affords makes it a very valuable agent for the introduction of an intratracheal tube.

"3 **Adjuvant to Other General Anesthetics**—Cyclopropane may be used as ether has been used in the past to supplement either ethylene or nitrous oxide, when either of these agents is not sufficiently potent to maintain adequate depth of anesthesia without anoxemia. The use of cyclopropane as a supplement to either of these agents will, of course, likely result in an explosive mixture. In the case of ethylene the addition of any considerable amount of cyclopropane to the mixture will necessitate an increase in the amount of oxygen which is being administered, and as a result the ethylene-oxygen mixture may reach a concentration that is explosive. In the case of nitrous oxide, this is because a reducing agent, cyclopropane, is added to 2 oxidizing agents, nitrous oxide and oxygen.

"4 **Supplement to Spinal Anesthesia**—There are many conditions which may arise during the course of spinal anesthesia in which cyclopropane is of great value. In our experience those in which it has proven itself of value are the following:

"(a) **Insufficiency of Spinal**—This insufficiency of spinal anesthesia may be due to (1) insufficient height, the anesthetic drug fails to reach a segment in the spinal cord high enough to render

anesthetic the entire field in which the operation is to take place (2) Insufficient sensory effect, with the use of very dilute drugs for spinal anesthesia such as a 1 1500 solution of nupercaine an occasional case will be encountered in which, although the patient has sufficient motor relaxation for the operative procedure, sensation is not completely abolished. (3) Insufficient duration, if for any reason the operation is of longer duration than was anticipated there is always the danger that the operation will outlast the anesthesia.

"(b) *Retching and Vomiting*—During the course of spinal anesthesia, retching and vomiting may be so persistent that the work of the surgeon becomes extremely difficult. Practically the only efficacious method of alleviating this condition is to administer a general anesthetic.

"(c) *Discomfort from Oxygen Administration*—When for any reason during the course of spinal anesthesia the administration of oxygen is indicated, the addition of a small amount of cyclopropane (just enough to insure unconsciousness) is of great value in alleviating discomfort to the patient from the pressure and the sense of suffocation caused by the face mask. This is particularly true if the patient is restless or nervous.

"(d) *Nervousness and Apprehension*—It is often necessary to render unconscious the very nervous, anxious or apprehensive patient.

"In all of these conditions in which a supplement to spinal anesthesia is of value, we found cyclopropane much superior to any other agent. The properties of this gas which render it particularly adapted to these cases are its potency, making it possible to give large amounts of oxygen, and the smoothness

with which induction is accomplished. Usually we are able to anesthetize the patient with cyclopropane for any of the above reasons without any change in the respiratory rate or volume, in fact the surgeon seldom is aware that a supplementary anesthesia is being used.

"5. Short Operations for Which Considerable Relaxation is Required

—For such procedures as orthopedic manipulations, setting of fractures (not in the presence of an x-ray machine), and pelvic examinations, cyclopropane anesthesia is very useful.

"6. *Abdominal Surgery*—Since we almost always use spinal anesthesia for abdominal operations, we are not in a position to evaluate cyclopropane for this type of surgery. We do feel, however, that the additional relaxation without anoxemia which cyclopropane affords, as compared to ethylene and nitrous oxide, will be greatly appreciated by surgeons who have been used to doing abdominal work under these last 2 anesthetic agents. On the other hand, surgeons who are accustomed to spinal anesthesia will probably not be pleased with the relaxation which cyclopropane affords. Cyclopropane stands between ethylene and ether in the degree of abdominal relaxation it produces. Perhaps it more clearly approaches the relaxation of ether.

"7. *Obstetrics*—Bourne, Griffith, Marvin and Saklad all report very favorably on the use of cyclopropane in obstetrics, for intermittent administration to relieve labor pains and for manual and instrumental delivery, as well as for the Cesarean operation. They report satisfactory working conditions for the surgeon, relatively low toxicity for the mother, and the very infrequent necessity for the use of any type of resuscitative procedure for the baby.

"We have had no experience with cyclopropane for any type of obstetrical procedure, but we would certainly expect that it would be particularly suited for this type of work, because of the large amount of oxygen which may be administered with it and because of its rapid, smooth induction."

INTRAVENOUS ANESTHESIA

Many anesthetists have found the acquisition of sodium thiopentobarbital (pentothal or sodium thionembital) and sodium N-methylcyclohexenyl-methylbarbituric acid (evipal soluble) valuable additions to the anesthetic armamentarium. Two of the greatest drawbacks heretofore to the further application of the drug have been: (a) The allusion to, in literature, to the experimental findings of cardiac irregularities occurring with the use of the thiobarbiturates in experimental animals and (b) the not occasional occurrence, during the administration of these drugs, of laryngospasm, coughing, and other respiratory complications

Cardiac Arrhythmias — A report from 2 of the members of the Anesthetic Staff of the New York University College of Medicine and Bellevue Hospital is very gratifying to those anesthetists who have never been able to demonstrate, clinically, in human beings, the occurrence of cardiac arrhythmias presumably due to the effect of the intravenous barbiturates' possessing a thio-radical.⁸ Gruber first claimed that the thio derivatives of barbiturate acids consistently produced cardiac irregularities in laboratory animals. Kohn found no such changes in animals during the use of sodium thio-pentobarbital. Reme and his coworkers found electrocardiographic alterations during anesthesia with pernorton and evipan but attributed these

changes to anoxemia rather than to the agent *per se*.

The Bellevue group has studied electrocardiographic tracings in 17 clinical trials during the use of sodium pentothal, evipal and sodium iso-amyl-ethyl-thio-barbiturate (sodium thio-ethyl-amyl). No deviations from the normal in these patients were found in the QRS, P-R interval, or T-waves. The increased heart rate which was observed was thought to be due to the action of the preliminary medication of morphine sulfate with or without atropine. The intravenous administration of neither epinephrine hydrochloride, nor ephedrine sulfate, during the course of these anesthetics, precipitated cardiac irregularities.

Respiratory Complications During Intravenous Anesthesia with Shorter Acting Barbiturates — Burstem and Rovenstine,⁹ while working with intravenous anesthesia with the shorter-acting barbituric acid derivatives in laboratory animals, noted laryngospasms and other respiratory complications quite frequently observed in human patients during the course of such anesthetics. This was especially true of the cat. In this animal, the vocal cords become adducted, and the laryngoreflex becomes hyperactive. Coughing is a frequent symptom. They interpreted these symptoms, which occur even under deep barbiturate narcosis, as being due to a central vagus stimulating action. To relieve this condition, they experimented with therapeutic doses of adrenalin, which were effective but transitory; therapeutic doses of ephedrine, which were not sufficiently effective; and lastly, neo-synephrin, which was not acceptable. It was recommended that derivatives of the atropine group (atropine or scopolamine) be used before the administration of these barbituric acid derivatives in order to prevent obstructive respiratory complications.

REGIONAL ANESTHESIA

The success or failure of regional anesthesia many times depends on the amount of care exercised with regard to minor details. An excellent general résumé of this aspect has been published by Woodbridge.¹⁰ He first demonstrates the importance of the proper use of the preanesthetic sedative drugs. Morphine should be given in liberal doses, but the drugs which are employed to allay fear, such as scopolamine and the barbiturates, should be used in small quantities, for large doses of the latter may cause the patient to become delirious and uncontrollable. It should be remembered, however, that the barbiturates also protect against, at least, the convulsant toxic effects of local anesthetics, and, for this reason, they should never be omitted.

Procaine has justifiably earned its popularity because of its many years of satisfactory use. Odom¹¹ agrees with Woodbridge in that metycaine appears, in many ways, to be superior. Its resulting anesthesia develops more rapidly, appears to be more intense and to last for a longer period of time. Its toxicity is very comparable to that of procaine. Either of these 2 drugs may be used in $\frac{1}{2}$ of 1 per cent and, occasionally, 1 per cent solution for local infiltration and for field block, and in 1 or 2 per cent solution for nerve block. The anesthetist himself should add the anesthetic agent and the vasoconstrictor drug to the saline solution, taking them from the manufacturers' labeled ampoules or from other reliable sources.

The possibility of the occurrence of toxic effects is greater with larger amounts of the drug than with small amounts, with stronger solutions than with weak, with hot solutions than with cold, with rapid injections than with slow; also, when these solutions are injected into regions well supplied with

blood vessels, as, for example, from the gums or from the sacral canal. The toxic symptoms produced are a fall in blood pressure, pallor, sweating, nausea and vomiting, and respiratory depression. Accidental intravenous injection may produce convulsions. Treatment consists of administering a vasoconstrictor drug and inhalations of oxygen. The last named complication (convulsions) may be controlled by the intravenous administration of a soluble barbiturate.

When epinephrine is added as a vasoconstrictor it may produce the undesirable effects of fear, rise in blood pressure and in pulse rate, pallor, and a fine tremor of the skeletal muscles. Injection should be stopped when these appear, and, when they have subsided, the injection continued with a solution containing a lesser quantity of the vasoconstrictor drug. In order to avoid these toxic symptoms it is suggested to employ 1 minum per ounce of 1 per cent solution and do not inject more than 80 cc of the 1 per cent solution or 200 cc of the 0.5 per cent solution without a pause of 10 minutes to allow signs of toxicity to develop.

Skin wheals may be made less painful by holding the needles with the bevel facing downward. If the needle must glide under the skin or over the surface of a bone the bevel should face toward the skin or the bone so that it serves as a sled runner. When making a subcutaneous injection the forefinger of the left hand should palpate the skin just ahead of the needle to serve as a guide. To avoid intravascular injection, not more than 1 cc of 1 per cent solution should be injected when the needle is stationary unless the aspiration test is performed. Needles should not be curved during their use as a precaution against breaking them. Also, the needle should not be advanced up to its hilt.

When the patient is under local or regional anesthesia, sharp dissection is preferred to blunt. Every effort should be made to avoid pressure and traction, and sponging should be done quite gently. The edges of an abdominal wound should be lifted upward rather than retracted laterally. He finally suggests that only those surgeons who find it acceptable to adopt gentleness and nicety of technic, which is required by local anesthesia, should attempt to work with it.

SPINAL ANESTHESIA

Dosage and Concentration of Spinal Anesthetic Drugs—A casual observation of the application of spinal anesthesia, especially where its use is a semiroutine one, makes it quite evident that the selection of the dosage of the anesthetic agent and its concentration as it is injected frequently does not receive sufficient consideration to insure maximum results. It has been suggested¹² that the following factors should be considered in the selection of the dosage of spinal anesthetic agents: (*a*) The blood pressure, and whether or not it is the patient's normal or whether or not it represents a change due to illness, (*b*) the location of the operation, (*c*) the duration of the operation, (*d*) the profoundness of relaxation required, (*e*) the patient's weight, (*f*) the length of the body, and (*g*) the age, vigor, nutrition and hemoglobin.

Diffusion methods require the use of a solution whose specific gravity closely approximates that of spinal fluid. Procaine crystals dissolved in spinal fluid is slightly heavier than spinal fluid itself, but may well be used for this method although its spread is somewhat influenced by gravity. A 10 per cent solution of procaine in water is practically isobaric and it is a very convenient and sat-

isfactory preparation. The dose is first measured in the syringe and then diluted with spinal fluid to the desired dilution and volume.

It is suggested that for the site of injection for inguinal, perineal, hip and lower extremity operations, except upon the knee, that the space between the third and fourth lumbar vertebra be used, except for very long operations when it is well to use a larger and more concentrated dose and deposit it between the fourth and fifth lumbar vertebra. The injection is made between the second and third lumbar vertebra for lower abdominal operations and between the first and second for upper abdominal surgery. For high stomach operations in tall individuals the space between the twelfth dorsal and first lumbar is occasionally indicated. When the higher spaces are employed, the concentration of the injected solution should be kept down to 3 per cent in order to avoid a too profound effect upon the intercostals, but the volume should be as large as possible to avoid too great an immediate dilution. In the space between the second and third lumbar, 4 per cent is ordinarily an acceptable concentration and, in the lower spaces, 5 or even 6 per cent may be employed. With higher than 6 per cent dilution there is a possibility of permanent damage to the spinal nerves or cord. Too high a concentration has probably been the cause of damage more often than injury by the needle. The amount of solution will vary from 2 or 3 cc. to 5 or 6 cc., according to the dilution used and the length of anesthesia sought.

When it is desired to decrease the dose and concentration due to age or debility or even smallness in size, it is often feasible to give what would seem to be an extremely small dose and at least partially make up for this in placing it 1 space higher than at first contemplated.

In vigorous individuals the dose may be considerably increased, and if a very long anesthesia is necessary a smaller volume of more concentrated solution may be placed 1 space higher or a larger total dose may be placed in the same or lower space. Failure to obtain anesthesia is due to failure to deposit the anesthetic squarely and entirely within the subarachnoid space. The solution should not be injected unless spinal fluid not only drips freely but also aspirates freely and rapidly.

Present Scientific Status of Spinal Anesthesia—In this presentation the author believes, in spite of the 2500 papers on the subject, that the field of spinal anesthesia is still governed more by empiricism than by scientific knowledge. He believes that much of the discussion of spinal anesthesia in the past has come from surgeons and that the major advance in knowledge in the future must come either from the experimentalist, who approaches the subject with an experimental objective, or the anesthetist, who is in a position to refute, confirm or qualify the conclusions of the experimentalist.

He shows a closer relationship between the length of the spinal column and the intradural volume than to its existence between the weight of the body and the intradural volume. Consequently, in order to determine the dosage of anesthetic drugs to be injected, he believed the length of the spinal column to be more important than the patient's body weight.

Co Tui^{13, 14} studied the hydrodynamics of spinal anesthesia by means of horizontal tubes which he observed in various positions. He also injected radio-opaque media into the subarachnoid space of experimental animals. As a result of these studies, he believes that the gravitational current induced by the

variation in weight between the spinal fluid and the injected anesthetic agent to be of greater importance than the diffusion factor. A second factor of importance is that of friction, which is present in children or in patients whose spinal canal is of small caliber. He believes that a long time is required for the attainment of a fixed concentration at any given level and that, therefore, so-called "fixation" is not as reliable as is now calculated. The draining of the heavier fluid into a dependent part may explain some cases of failure of analgesia. In this case, the analgesia will be of a segmental type occurring in regions supplied by the nerves in a more dependent portion. In animals, when the respiratory center is depressed or paralyzed there is an asphyctic rise of blood pressure which continues until the asphyxia is overcome or until the animal dies of circulatory failure. There is no fixed paralytic dose on the respiratory center; the health of the animal influences this factor. When paralysis of respiration occurs, the paralysis is reversible and, if artificial respiration and the blood pressure level are maintained until the drug is destroyed or eliminated, the respiratory excursions are restored. Another form of cessation of respiration may be due to cerebral anemia as a result of the hypotension.

Whether there is respiratory center depression or paralysis or peripheral paralysis, there is embarrassment of respiratory movement. This leads to anoxia and accumulation of carbon dioxide in the blood. Carbon dioxide over certain concentrations is of itself toxic to an otherwise normal organism. In the presence of paralysis of the sympathetic nervous system, as in the spinally anesthetized animal, carbon dioxide presents a special toxicity—it lowers the

blood pressure by peripheral capillary dilatation. It is by this mechanism that it may be shown that carbon dioxide is dangerous as a respiratory stimulant in spinal anesthesia.

Regarding the effects of spinal anesthesia on the circulation, it is believed that the fall in blood pressure is due to a vasoconstrictor paralysis, not only of the splanchnic area but of the whole area supplied by the paralyzed spinal nerves. The evidences of this are many and include a fall in the blood pressure accompanied by an increase in the volume and a rise of the temperature of the posterior extremities, a lowered vasomotor tone and an enlargement of the spleen 2 to 7 times its normal size. Co Tui believes that the spinally anesthetized animal may be a badly handicapped animal. "His respiratory system may be crippled by thoracic paralysis and his circulatory system by an inability to compensate, while the paralysis of his adrenaline secretion incapacitates his mobilization of sugars, as well as of fibrinogen. The degree of decompensation is, however,

relative, depending on the volume of the body which has been paralyzed and thus put beyond the control and regulation of the co-ordinating nervous system"

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ENDOSCOPY

By LOUIS H. CUTRE, M.D.

BRONCHOSCOPY

Bronchoscopy for Diagnosis

The advantages of bronchoscopy for diagnosis of obscure chest signs and symptoms would be greatly enhanced if the internist was capable of thinking clearly in terms of bronchoscopy and the bronchoscopist was familiar with diseases of the chest. Considered as an important adjunct in diagnosis, it permits one to observe, during the patient's life, pathologic processes and associated mechanisms of the tracheobronchial tree.

In reviewing the indications for bronchoscopy one must consider broadly the occurrence of obstructive emphysema and obstructive atelectasis, the presence of pulmonary lesions that cannot be explained by the usual diagnostic aids, unexplained cough, wheezing respiration, unexplained hemoptysis and dyspnea.

Tracheal Stenosis from Irradiation

While there may be justification for complications following intense irradiation in the treatment of carcinoma, there is grave question concerning the desir-

ability of employing such measures in great amount as a form of elective treatment for conditions compatible with life. Clerf and Putney¹ discussed this question and reported 2 cases of exophthalmic goiter which were treated by irradiation and later developed disabling tracheal lesions without laryngeal involvement. In one case tracheotomy became necessary for obstructive dyspnea. A granuloma found partially occluding the trachea was removed bronchoscopically (Fig. 1) In a second case there was tracheal stenosis with atrophic mucosal changes and crusting. Cough was troublesome and at times dyspnea was distressing. The prognosis in this case was not considered favorable owing to the extensive atrophic changes, however, there has been some improvement under local treatment. Inquiry might be made if irradiation has a place in the treatment of exophthalmic goiter and, if so, could proper precautions be exercised to avoid trophic reactions which are disabling and may terminate fatally.

Neoplasms of Trachea and Bronchi

The absence of early symptoms undoubtedly accounts for delay in the diagnosis of carcinoma of the trachea. The ready accessibility of the trachea to direct examination should lead to early diagnosis if disease is suspected.

Culp² collected a series of 433 recorded cases of primary tracheal neoplasms, 34 per cent of which were carcinomata, and added 2 personal cases. The available autopsy statistics indicate the infrequency of primary malignancy of the trachea. The squamous cell variety and adenocarcinoma are equally common. There seems to be a predominance of males affected by this disease, which usually originates in the lower one-third of the trachea, particularly on the posterior wall. Metastasis occurs early in any of

the tissues or organs of the body, resulting in a very poor prognosis regardless of method of treatment instituted.

Gebauer³ reported a case of osteochondroma of the right lower lobe bronchus occurring in a man aged 44 years. Although there was a history of frequent colds, the occurrence of severe hemoptysis for a period of 5 days directed attention to the presence of disease of the



Fig. 1—Drawing of granuloma found partially occluding the lumen of the trachea. The surface was smooth. The point of attachment was anterior. (Clerf and Putney. *Ann Otol Rhinol and Laryngol*, Sept., 1938.)

chest. The tumor almost completely occluded the right bronchus and appeared as a hard corrugated mass. Following its removal by bronchoscopy there has been no evidence of recurrence.

Carcinoma of the Bronchus—The largest single series, 164 cases, of carcinoma of the bronchus reported to date is that of Stem and Joslin⁴. They note an increase in the number of cases of bronchial carcinoma recognized but whether real or apparent is still speculative. Obstruction of the bronchus with its associated pathological changes accounts for the usual symptoms, and is demonstrated roentgenologically most commonly as some degree of atelectasis. It is of interest to note that of the 164 cases a diagnosis was established by postmortem examination in 100 cases and by bronchoscopy with biopsy in but 21 cases.

These cases studied either by histologic or postmortem examination revealed an almost even distribution of cancer cells between the squamous, glandular and undifferentiated varieties. Since most of

In a study of 100 consecutive cases of carcinoma of the bronchus in which the diagnosis was made bronchoscopically on the basis of biopsy, Ormerod⁵ found that in 62 the growth was a squamous cell



Fig. 3.—Roentgen ray of chest showing lower two-thirds of the right lung obscured by dense shadow with heart and mediastinum drawn to the right (Baum *Ann. Int. Med.*, Nov., 1938.)

the growths originate in the larger bronchi, surgical treatment generally necessitates total pneumonectomy. The large number of far advanced cases that are seen can be given only irradiation therapy as a palliative measure.

and in 38 a nonsquamous cell carcinoma. The 2 types were found to occur with equal frequency in all 3 zones of the lung and to pursue practically the same clinical course. While the number of cases of successful lobectomy and pneumonectomy

is increasing, in a large majority of Ormerod's cases the growth was found to be too far advanced to permit of the employment of these procedures. It was therefore found necessary to attempt its

which can be left in the bronchus for a long time and then removed. The advantage of radon seeds is that they may be introduced directly into the tumor instead of being placed alongside it in the

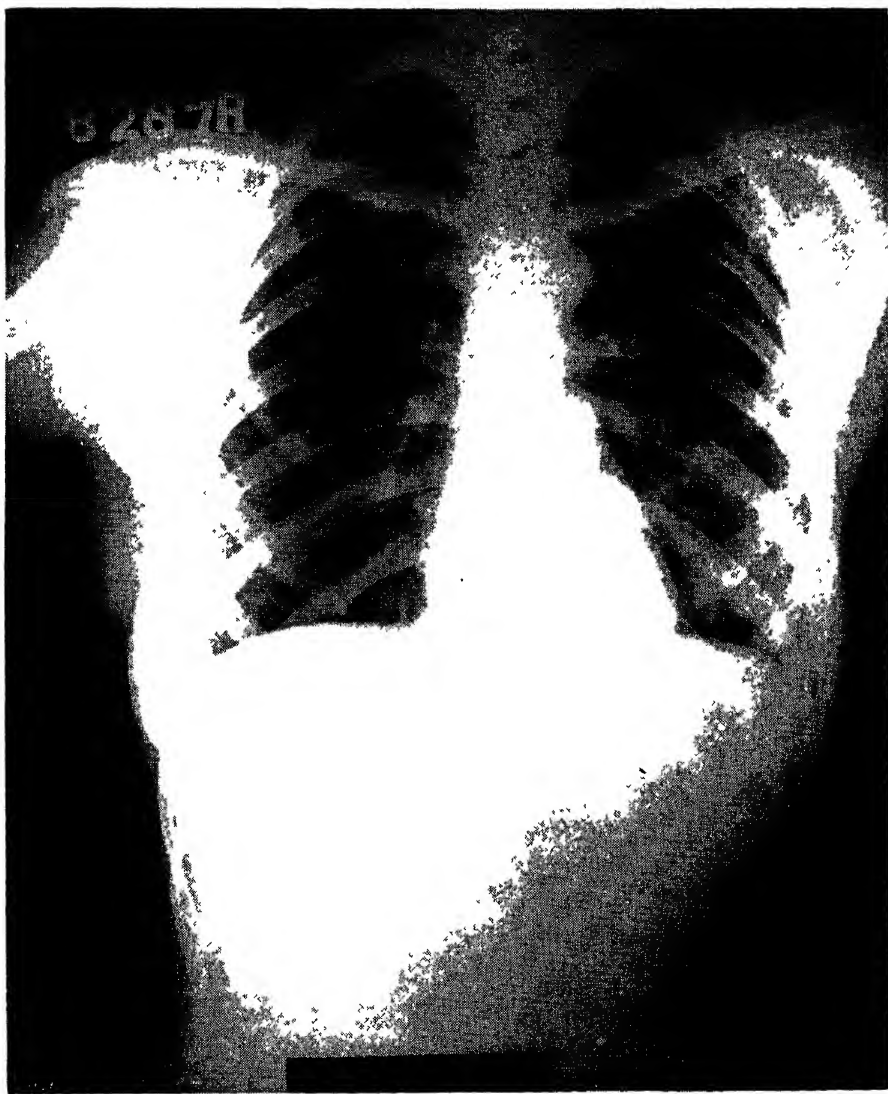


Fig. 3—Roentgen ray made 5 days later showing rapid return to normal of the right lung after bronchoscopic removal of the obstructing growth (Baum Ann Int Med, Nov, 1938)

destruction by less radical measures. The method which has been largely followed by the author is the introduction of radon into the bronchus. Radon seeds may be inserted directly into the tumor or they may be applied in some form of container

bronchial lumen, they can be distributed in distant portions of the growth, and they are more likely to remain in position. When one considers the type and the inaccessibility of the growths in the cases reported, the results appear very

satisfactory. The average life of the untreated patients was $3\frac{1}{2}$ months and that of the treated patients $7\frac{1}{5}$ months.

Primary Sarcoma of the Lung —

This is a very rare tumor. It commonly has its origin in peribronchial or interalveolar connective tissue and therefore is not often observed as a bronchial tumor. Stenosis of the bronchus when present usually is compressive in origin.

The case reported by Baum and others⁶ exhibited chest signs of obstructive atelectasis of the right lower lung indicating that there was present obstruction of the right bronchus. The patient, a woman, aged 29 years, had been ill for 6 weeks. A diagnosis of pneumonia and pleurisy had previously been made. There was fever with cough, slight sputum, never blood tinged, and sharp pains in the right chest. Roentgen studies of the chest corroborated the clinical diagnosis of obstructive atelectasis (Fig. 2).

At bronchoscopy there was found soft friable polypoid tissue occluding the right main bronchus. Practically all of the tissue was removed with forceps and suction. There was striking improvement in the chest signs, within 24 hours after bronchoscopic removal of the growth the right lung appeared normal by physical examination and fluoroscopy. A roentgen film made 5 days later revealed a normal chest (Fig. 3). The histologic diagnosis was spindle cell sarcoma. Irradiation therapy has been instituted but too little time has elapsed to warrant an expression regarding the prognosis.

Bronchoscopy in Tuberculosis

Warren⁷ and his associates reviewed the results of bronchoscopic examination in a series of 198 tuberculous patients. Of the 74 patients found to have tracheobronchial tuberculosis the majority of the lesions existed either as granulation

tissue or discrete ulceration. Other forms including cicatricial stenosis, ulcerostenosis, tuberculomas, and diffuse mucosal inflammation were noted. Local treatment seems to have benefited the patients and the authors advocate 3 methods, namely cauterization of the ulcerating or granulating ulcerations, removal of tuberculomas and dilatation of the stenoses. There were 6 deaths recorded and these appear to have been due to the extent of parenchymal involvement rather than the severity of the bronchial disease. Fifty-seven cases of tuberculous bronchitis or tracheitis were treated. Of this number 34 healed, 10 progressed or did not improve and 9 still are under treatment. The remaining 4 cases either refused treatment or were too ill to have treatments continued. In their experience tuberculous tracheobronchitis responded favorably to electro-surgical and chemical cauterization. There were 31 patients in whom the sputum was positive in spite of the apparent control of the parenchymal disease. Healing of the bronchial lesion was followed by prompt sputum conversion in 22 out of the 26 cases.

While evidence of bronchial obstruction constitutes a majority of the indications for bronchoscopy the authors are agreed that hemoptysis unexplained on the basis of peripheral lesions or presence of acid-fast bacilli in the sputum and variations in the amount and character of the sputum can be considered as definite indications for bronchoscopy.

Several methods of approach for the treatment of tuberculosis of the trachea and bronchi have been suggested by Kernan.⁸ Treatment of ulceration of the tracheobronchial tree is directed towards prompt healing with the formation of a minimum amount of scar tissue. To accomplish this, immobilization of the lung by *pneumothorax* and direct treatment of the ulcerated area, preferably by the

mercury vapor lamp, is recommended. Tuberculous strictures are either closed by **coagulation**, provided the lung distal to the stenosis is dry, or **dilatation** may be used to insure a patent bronchus and drainage of the secondary infection. Obstructing tuberculous tumors should be removed by coagulation. Tumors may be pedunculated, producing obstruction, causing a flapping sound during respiration. These are best treated by **coagulation**, thus avoiding stripping of the mucous membrane. Tuberculous tumors may also produce obstruction to a bronchial orifice with resulting obstructing emphysema or obstructive atelectasis. It is important to be aware of this when contemplating pneumothorax therapy, for in the presence of obstructive emphysema it may not be possible to compress a lobe or lobes.

Reduction of involved lymph nodes may be accomplished by **roentgen-ray therapy**; spontaneous rupture of a suppurating node requires **aspiration**, and solid portions necessitate **removal** as any other foreign body. Kernan also brings up the question of incision through the bronchial wall to allow drainage of tuberculous mediastinal abscesses or removal of obstructing mediastinal nodes. In some cases **pneumonectomy** must be considered.

Davison⁹ has employed an electrocoagulation current of weak intensity in the treatment of tuberculous tracheobronchitis with uniformly good results. A total of 8 patients were treated. In all of these the lesions had been present for some time and exhibited little tendency to heal. No harmful effects were noted as a result of the bronchoscopic treatments, which were carried out at intervals of 2 to 4 weeks. There were no laryngeal complications, and no spread of the parenchymal lesion was observed. In each case there was a consistent tend-

ency for the lesion to heal. Six cases are clinically well; 1 patient still under treatment is improving rapidly. Treatment was discontinued in the remaining case because of the patient's extreme debility, although there was regression of the bronchial lesions under treatment.

In summing up his experience with bronchoscopy in tracheobronchial tuberculosis, Myerson¹⁰ expressed the opinion that bronchoscopy is of value principally as a diagnostic procedure in tuberculosis of the trachea and bronchi. The bronchoscopist is able to localize the cause of the atelectasis by finding an obstructing tuberculoma or fibrotic lesion. He can take smears from each bronchial orifice to ascertain the lobes from which the positive sputum is coming. Except for coagulation and cauterization of tuberculomata and the searing of inactive ulcers, there is little of positive value that the bronchoscopist can do in these cases. Silver nitrate should not be used in solutions stronger than 5 per cent; 10 per cent or stronger has a destructive effect. Strictures cannot be dilated because of the type of cicatricial tissue which is present and because of their length. The average dilator is easily broken by the resistance of these firm fibrous stenoses. In addition the possible presence of an active lesion in the subepithelial and peribronchial tissues makes dilatation dangerous. Aspiration is of value for the removal of secretions which are retained beyond obstructive lesions in the bronchi. Unfortunately this procedure has only temporary value, since the secretions reform within a few hours, and bronchoscopy at intervals frequent enough to keep the involved area clear is not practical. Ultimate healing and recovery depend more upon the ability of the tissues to react and heal than upon the therapy employed.

Postoperative Complications

Haight¹¹ considers the employment of constant intratracheal suction as essential in the prevention and treatment of postoperative pulmonary complications. Unsuccessful conservative measures to facilitate bronchial drainage have been followed by either bronchoscopy or aspiration through an intranasal catheter. Ineffectual cough or retention of secretions are sufficient indications for mechanical bronchial suction. Mention is made of the judicious use of drugs, particularly narcotics, and the importance of posture in the prevention of pulmonary complications.

In a study of the pathogenesis of postoperative pulmonary atelectasis, Iglaue¹² was unable to discover any factors that might aid in explaining the occurrence of atelectasis after tonsillectomy under local anesthesia in a patient observed by him. The patient, aged 18, was given morphine sulfate, $\frac{1}{6}$ gram (0.01 gm) with atropine sulfate preliminary to operation. Local anesthesia was induced with procaine hydrochloride in a 1 per cent solution. Within 24 hours there was evidence of collapse of the lower part of the right lung. Use of the bronchoscope was resorted to, and 3 cc of mucopurulent material was removed. The patient made a complete recovery. Iglaue suggested a possible relation between the occurrence of atelectasis and posttonsillectomy pulmonary abscess.

ESOPHAGOSCOPY

Postcricoidal Carcinoma

In reporting the occurrence of postcricoidal carcinoma in a woman, aged 54 years, Johnson¹³ emphasized the importance of the history in these cases. In his case there was dysphagia for more than 25 years. The patient always had been

frail and underweight and had been treated for anemnia over many years. There was a history of dental trouble and the last teeth were extracted when she was 41 years old. Seven years previously a web in the upper esophagus was discovered at esophagoscopy. There



Fig 4 -Roentgenogram of the esophagus before treatment shows almost complete obstruction in the lower third of its lumen (Benedict New England J Med, April, 1938)

were fissures at the corners of her mouth and the tongue was smooth. The history and the findings exclusive of the postcricoidal carcinoma are those observed in Plummer-Vinson syndrome. Owing to the pathologically altered mucosa this syndrome should be considered as a pre-cancerous state. Johnson emphasized the importance of recognizing the symptoms of dysphagia, hypochromic anemia, atrophic changes of the mucosa of the lips, mouth and tongue, fissuring at the angles of the mouth, early loss of teeth, frequent changes in the nails and splenomegaly

as Plummer-Vinson syndrome, a precancerous state, and the need for prompt and appropriate treatment. The predisposition of females to this syndrome and postcricoid carcinoma suggest a relationship and should emphasize the possibilities in cancer prevention.



Fig 5—Roentgenogram of esophagus after esophagoscopy bouginage shows free passage of barium through the previously stenosed lumen (Benedict *New England J Med*, April, 1938)

Cicatricial Stenosis

Attention was directed to the development of esophageal structure complicating duodenal ulcer by Benedict and Daland¹⁴. Their patient developed an acute esophagitis in the lower one-third of the esophagus 5 weeks following gastric resection for duodenal ulcer. There was an absence of substernal pain and the appearances of the esophagus both by roentgen examination and esophagoscopy suggested that the stenosis followed acute esophagitis rather than a peptic ulcer of the esophagus (Fig. 4). Esophagoscopy

bouginage was instituted and dilation was secured quite promptly so that the patient was able to return to a liquid diet and later could swallow soft food. Dilation has advanced to a point where a 7 mm. esophagoscope can be passed through the stricture; esophagoscopy is being continued (Fig. 5).

GASTROSCOPY

Prior to 1932 gastroscopy was not considered to be a particularly safe procedure for general diagnostic employment and was carried out by a relatively small group of workers. The development in 1932 of a flexible gastroscope which could be employed with safety and permitted the examination of practically the entire interior of the stomach renewed interest in this procedure. Flexible tube gastroscopy was introduced into this country during 1933. It has gained great popularity and now is being employed quite generally as a diagnostic aid. In addition there is developing an extensive literature on the subject.

Gastroscopy for Diagnosis

Direct visualization of the stomach affords the best means of recognizing gastritis. In recording their findings Gaither and Borland¹⁵ believe that the simplest working classification is that of Schindler, with its divisions of superficial, atrophic, and hypertrophic forms. Because of the wide variety of changes in the gastric mucosa and insufficient pathologic control, it has been impossible to establish from gastroscopic appearances criteria by which disease entities may invariably be recognized. Most gastritis stomachs show definite activity. There are evidences of inflammation, hypertrophy, ulceration, hemorrhage and localized injection. This includes the superficial and hypertrophic groups. In

a small percentage of cases the lesion seems inactive and atrophied, corresponding to the atrophic form of gastritis.

The appearances of the postoperative stomachs were all definitely congested; the most marked cases of atrophy were observed in pernicious anemia



Fig. 6—Gastroscopic appearances of syphilis of the stomach before treatment. (Carey and Ylvisaker, *Ann. Int. Med.* Oct. 1938.)

Submucosal hemorrhagic areas have been observed in about 7 per cent of cases. The significance of these has not been determined.

Direct visualization of the interior of the stomach forms an adjunct in diagnosis and Moersch and Snell¹⁶ point out its value when combined with clinical and roentgen findings. Gastroscopy should be utilized when there is any discrepancy in the routine studies, when roentgen findings demonstrate a lesion the nature of which is not apparent, or if roentgenologic examinations cannot explain the persistence of postoperative symptoms. Likewise, the progress of gastric lesions under a medical regimen can be closely followed. Clinical interest in all forms of gastritis has been stimulated by the frequency with which this

condition is found gastroscopically. While the diagnosis of moderately advanced carcinoma usually can be made by roentgen examination there may be difficulty in the early stages. In this type of case gastroscopy is of definite value in establishing the nature of the lesion and also in giving information regarding its operability. While the endoscopic appearances of carcinoma vary, they usually are sufficiently characteristic and can hardly be mistaken for a benign ulcer or one of the rare benign tumors of the stomach.

Although it has long been recognized that hemorrhage may occur with gastritis, the more general employment of gastroscopic examination in cases of this condition has revealed that gastritis is an important cause of gastric bleeding. Benedict¹⁷ used the gastroscope in a study of 20 cases of acute or chronic gastritis associated with hemorrhage. The only demonstrable and the most probable source of bleeding in these cases was the superficial or hypertrophic gastritis present, often with one or more erosions in the gastric mucosa. An important etiologic factor in massive bleeding from gastritis is the excessive use of alcohol. In Benedict's opinion a varying degree of bleeding from chronic superficial or hypertrophic gastritis may occur in the absence of other demonstrable changes in the gastrointestinal tract. Gastroscopic examination is indispensable for the accurate diagnosis of gastritis and the recognition of erosions.

According to Carey and Ylvisaker¹⁸ English medical literature contains no gastroscopic description of gastric syphilis of the linitis plastica or leather bottle type. They reported the case of a man, aged 64 years, without gastric symptoms whose complaints were weight loss and pains in the lower extremities. Serologic reactions for syphilis were strongly positive. Gastric analyses showed decreased

or absent acid content. A diagnosis of *limitis plastica* was made on the roentgen-ray examination of the gastrointestinal tract.

At gastroscopy the lumen of the stomach appeared to be contracted. The normal anatomical landmarks and all normal folds and rugations were effaced and were replaced by broad, thick folds and indentations. The pyloric opening was of irregular shape, tending to be slit-like and partly open. The antrum appeared as a stiff, almost tubular structure, irregularly creased and indented and pinkish in color (Fig. 6). Under appropriate antiluetic treatment there was progressive restoration to the normal gastric appearances (Fig. 7).

Chevallier and Moutier¹⁹ found gastroscopic examination an invaluable aid in the diagnosis of anemias. They agreed with Schindler and his associates with regard to its use in discovering new lesions. A color relationship exists between certain changes in the blood and alterations in the gastric mucosa. These changes are distinctly different in hypochromic anemia and in the anemias of the pernicious type. Whereas in hypochromic anemia one finds only slight diffuse atrophy, in the pernicious anemias the atrophy is more marked and more generalized and pearly plaques can be seen. These changes are so clear that if one makes a gastroscopic examination on a subject presenting any digestive disturbances, it supplements other examinations in detecting associated diseases of the blood. Gastroscopic examination enables one to determine the alteration of the gastric lesions associated with the anemias, by demonstrating the initial step. Gastroscopic examination shows that repair of the mucous membrane is possible; the alteration of the blood picture and the repair of the mucous membrane go hand in hand. While the hemo-

gram of a patient with pernicious anemia shows hyperchromia in the beginning, hypochromia frequently develops under the influence of liver therapy. One sees the mucous membrane lose its pearly color and the atrophy becomes that of the common type seen in hypochromic

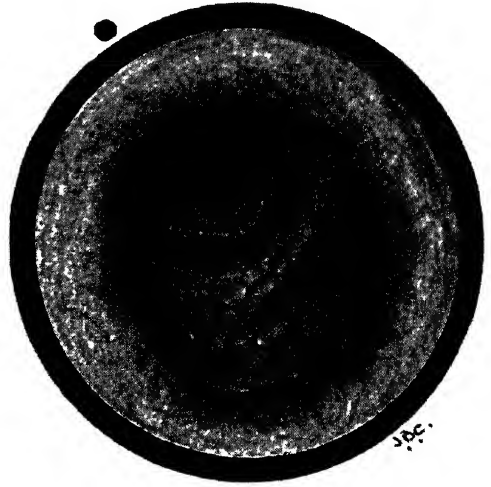


Fig. 7—Gastroscopic appearances of syphylis of the stomach after treatment (Carey and Ylvisaker. *Ann. Int. Med.*, Oct., 1938.)

anemia. Study of the mucosa allows one to see a veritable rebirth of the epithelium and a re-formation of villi. The re-formation of the villi is clearly shown by small red dots, like the tip of a gloved finger, seen at repeated intervals. These dots must represent tortuous and dilated capillaries in the newly formed villi.

Endoscopic examination also allows one to give a prognosis on the degree of repair of the mucosa, regardless of the apparent general condition of the patient. Gastroscopic examination is helpful in diagnosing other diseases of the blood. It allowed the authors to discover an autonomic gastric purpura. Gastroscopic studies carried out simultaneously with hemologic studies permitted the fitting of the condition of the stomach into the general pathologic changes of the anemias.

These studies suggest that, in spite of the importance of the stomach in pathologic changes in diseases of the blood, the condition of the stomach is not the cause of certain of these diseases; rather, the stomach is affected to the same extent as the blood by a general morbid factor.

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GYNECOLOGY

By P. BROOKS BLAND, M.D., and ARTHUR FIRST, M.D.

BLADDER

Pyuria

The treatment of pyuria with *mandelic acid* is discussed by P. Summerfeldt and A. Brown¹. During the last 17 months these investigators treated 52 cases of infection of the urinary tract with sodium or ammonium salt of mandelic acid. Of these, 31 cases were acute pyuria and 21 were persistent pyuria. The organisms present in the urine were *Bacillus coli*, except in 6 cases in which they were *Bacillus paracoli*, 2 cases in which they were *Staphylococcus aureus* and in 2 cases dysentery, 1 of which was a *Bacillus flexneri*. Not 1 of these organisms was resistant to treatment. Of the 40 patients treated with sodium mandelate and ammonium chloride the urine of 50 per cent was free of pus and bacteria in from 1 to 7 days after the reaction of the urine was

more acid than a pH of 5.8. In 38 per cent, sterile urine was obtained in from 8 to 34 days, while in 12 per cent there was no response to treatment. Of the 12 patients treated with ammonium mandelate, 58 per cent responded to the drug within 7 days, while 42 per cent required from 9 to 28 days. The patients with acute pyuria responded to treatment more quickly than did the persistent group. Twenty cases were observed for from 1 to 16 months. There was a recurrence of the pyuria in 4 cases, and of bacilluria in 3 cases. In 13 cases there was no recurrence of either the bacilluria or the pyuria.

Urinary Tract Infections

E. Schnohr and C. Johansen² used *calcium mandelate* in the treatment of 60 patients with infections of the urinary tract. The dose was 12 Gm. daily and the amount of fluid ingested was limited

to 1 liter daily. In 39 cases the urine became sterile, in 31 after a week or less, in 5 after from 9 to 13 days, in 3 after 20, 25 and 65 days respectively. In 13 cases the subjective symptoms disappeared although the urine did not become sterile. The treatment was without effect in 8 cases (6 with complicating disorders, 1 with a history of ureterotomy, 1 in a pregnant woman given only 2 days' treatment). The urine became sterile in 7 of 20 patients in whom the infection was a complication in a grave disorder of the urinary tract and in 8 of 13 cases with milder complications. The bacillary infection was eliminated in 34 of 47 cases with *B. coli* infections, in 2 of 9 cases with *B. proteus* infection and in some cases with infection with staphylococci, gram-positive cocci and hemolytic streptococci.

In most cases the pH in the urine was reduced to between 4.8 and 5.3. As a rule the urine did not become sterile until the pH was 5.3 or less; it was never sterile when the pH was over 5.5. In 6 cases in which the pH remained between 6 and 8 the addition of from 3 to 6 Gm. of *ammonium chloride* daily brought the pH to about 5 in 4 and the urine became sterile in 2. Except for a transitory hematuria in 1 instance, treatment with calcium mandelate caused no injurious effect on the kidneys, although the renal function was impaired in several cases. Only 2 patients were unable to take the granulate because of gastric symptoms. Occasionally nausea occurred after some days' treatment and in 2 cases there was nausea during the first days.

Urinary Antiseptics—A discussion of local urinary antiseptics is presented by H. W. E. Walther.³ The substances used in local antiseptic treatment of the urinary tract fall, in a general way, into groups of (a) *mercurials*, (b) *silver*

salts, inorganic and organic, (c) *dye therapy* and (d) *chemotherapy*, although the members of these groups overlap at some points. In addition, and not falling precisely into any 1 of the groups, there are such time-honored remedies as *potassium permanganate*, *boric acid*, *phenol*, *cresol*, *trinitrophenol (picric acid)* and various other more or less widely used drugs.

Acridavine (U. S. P.) — Neutral acridavine is a popular drug now in common use. When properly diluted it is not irritating, and in selected cases its use has given extremely satisfactory results. If used in too strong concentration it readily invites stricture, owing to chemical inflammation of the tissues. It is ceceptive, and many patients will not tolerate it. Too long continued or too frequent use is also to be avoided. One injection a day is all that should be risked.

Mercurochrome (N. N. R.) — This dye has been decidedly popular for a good many years as a urinary antiseptic for local use. If administered in low dilution not more than once a day for not more than 3 days in succession it is not irritating.

Gentian Violet Medicinal (N. N. R.) — This is 1 of the rosaniline dyes, with low toxicity for the tissues and excellent capacity for penetration. Its relative harmlessness has been proved by the observation that tissue cultures are not injured by concentrations that arrest bacterial growth. It is particularly successful in anterior urethral infections of a nonspecific nature.

Potassium Permanganate (U. S. P.) — This most common of all antiseptic astringents acts directly on the gonococcus. It has in addition an indirect action by causing edema of the mucosa of the urethra, which helps to destroy the organism. In the presence of organic

material, potassium permanganate is rapidly reduced to inactive manganese dioxide, setting free nascent oxygen. It is during this process that the gonococcal action occurs. It should be used as hot as the tissues can bear.

Boric Acid (U. S. P.)—Although in reality not germicidal, boric acid is such an admirable cleanser that no discussion of this kind would be complete without including it. The absence of all toxic effect makes it an ideal irrigating fluid where bulk is desirable for cleansing or distention.

Silver Nitrate (U. S. P.)—The inorganic salts of silver, of which silver nitrate is the best known and most useful, form resistant precipitates with proteins, so that their local action is easily controlled. The antiseptic effect of silver nitrate is high, its toxicity low. In the presence of the tissues of the body, silver surpasses mercury, since its protein compounds, as well as the colloidal oxides and metallic silver, liberate a small amount of silver ions. The antiseptic action of silver nitrate goes quite deep, since it forms easily soluble double salts of silver albummates and sodium chloride in the tissues. Its caustic and astringent action may be stopped with sodium chloride. It acts on the urethra by liberating nitric acid and coagulating albumin. It also exerts an indirect influence in stimulating the mucous membranes wherever it is introduced into the urinary tract. A reaction is necessary in the form of slight burning. This irritant character contraindicates its use in some cases but increases its value in others. If any chlorides are present in the urine, it is immediately precipitated in the form of inactive silver chloride. This makes its action on the urinary tract only momentary. It should therefore be reserved for cases in which an irritative or caustic effect is desired.

Strong Protein Silver (U. S. P.)—These proteates have the lowest percentage of silver (from 7 to 8.5 per cent), but in solutions this becomes largely ionized, so that they have the strongest bacteriostatic effect but are also distinctly irritant, though far below silver nitrate in this respect. The irritant effect of this preparation, originally introduced under the name of protargol, is about one-tenth that of silver nitrate, confirming the fact that nearly all the silver is ionized. All these colloidal silver preparations consist of finely divided metallic silver in colloidal suspension with a protective colloid of some albuminoid substance to maintain the suspension. They apparently do not penetrate deeply but have a definite antiseptic value on mucous membranes.

Mild Protein Silver (U. S. P.)—With slight variations this group contains such preparations as argyrol, neosilvol and other colloidal compounds of silver oxide and a protein derivative. It differs from strong protein silver in being entirely nonirritant. It is also less active as an antiseptic but more soothing. The high specific gravity of its solutions facilitates their spreading, enabling them to act as detergents for the removal of pus and secretions.

Urethritis in the Female—In gonorrheal urethritis the remedies are applied by swabbing instead of by injections and are used in greater strength, from 1 to 10 per cent **strong protein silver** or from 0.5 to 2 per cent **silver nitrate** every second or third day. **Potassium permanganate douches** are given.

Nonspecific urethritis in women is usually called cystitis, since the infection is bound to reach the bladder. The cause of this condition is nearly always traumatic. Instillations of **mild protein silver** from 5 to 10 per cent or of

strong protein silver from 1 to 2 per cent afford some relief, **mercurochrome** from 0.25 to 1 per cent is also used here. Topical applications of silver nitrate from 5 to 75 per cent through the endoscope, although painful, serve to open up the ducts and allow the pent-up secretions to come away. They should not be repeated too often, however. Careful examination in these cases reveals that the primary inflammation is in the small posterior urethral glands. Instillations of mild protein silver from 10 to 50 per cent have also been found beneficial.

In the most acute stage of cystitis, no local treatment is undertaken. A little later treatment with instillations of mild protein silver may be begun, from 25 to 50 per cent of the mild or from 1 to 2 per cent of the strong. Before instillation the bladder should be completely emptied by voiding, then **irrigated** with plain sterile water, hot boric acid solution or physiologic solution of sodium chloride. Another useful instillation is mercurochrome 1:100, left in the bladder as long as tolerated.

Bladder irrigations, also begun a little later, and preceded by lavage with boric acid or sterile water, may be done with any of the following: Silver nitrate, 1:10,000 to 1:5,000; potassium permanganate, 1:8,000, acriflavine, 1:8,000.

Since silver nitrate is an irritant, its use should be preceded by as well as followed with application of a surface anesthetic such as metycaïne. Such irrigations are useful in acute cystitis, provided there are no stones or malignant growths. The dyes may sometimes safely remain in the bladder for 2 or 3 hours. If the inflammation is due to some condition producing stasis, such as a stone or a tumor, local treatment will not correct it. Silver nitrate will sometimes clear up cystitis so effectively that its

action appears almost to be specific. Since in the strength used (1:10,000) it is not an antiseptic, any action it exerts must be due to some reaction within the mucous membrane.

Nonspecific cystitis without renal or urethral involvement responds well to daily instillation of mercurochrome from 0.5 to 1 per cent, especially in the female. In gram-positive infections of the bladder, irrigations of gentian violet from 1:10,000 to 1:5,000 or instillations of 1 per cent or more have a specific effect on the staphylococcus and certain other types of local infection.

In *chronic cystitis* the usual treatment is **distention irrigation** with **silver nitrate** from 1:10,000 to 1:1,000, after the bladder has been washed with a 2 per cent boric acid solution or distilled water; also instillation every other day of from 1 to 2 per cent silver nitrate, if not too painful. Otherwise, one of the silver proteins may be used. **Potassium permanganate irrigations** 1:8,000, used hot, are frequently beneficial. Mild protein silver from 10 to 15 per cent or strong protein silver from 0.25 to 2 per cent as an irrigation is widely employed. Some urologists still make use of **mercury bichloride** 1:30,000 for irrigation of the bladder. **Mercurochrome** 0.25 per cent and **acriflavine** from 1:10,000 to 1:5,000 are all used, and all give good results as irrigations in properly selected cases. 1:8,000 acriflavine dilutions have been found effective in bladder conditions secondary not only to acute gonococcal urethritis but also to nonspecific urethritis.

CERVIX UTERI

Carcinoma

N. F. Miller and C. E. Folsome⁴ pessimistically question whether radium is a cure-all for the very early case of

cervical malignancy. In advanced cancers of the cervix, radium, they agree, holds a place of undisputed supremacy. Through its proper use countless doomed women are granted years of life. Among this group there is little reason for questioning its value. It is to the minority, the small group of early, favorable cases, that their question applies. With the 8-, 10-, and 15-year follow-up reports of the pioneers in this field comes the growing suspicion that what is good for the last case is not necessarily good for the early case. The revelation that early cases treated by radiation when followed over a decade or more continue to show a progressive death rate from cancer cannot be viewed without concern. Among this early group there exists at least 1 other method of treatment. Perhaps the swing from surgery to radium and x-ray has been too complete for the good of all concerned. Unless prolonged follow-up study of early case treated by means of radiation can show permanency of cure equaling that of surgery, it would appear that, for these early cases, a return to surgery of adequate character is highly desirable.

K. H. Martzloff⁵ discusses his experience for the past 7½ years with the colposcope and the iodine test in the recognition of incipient cancer. The iodine test is not specific for cancer or for areas of so-called probable beginning cancer. Schiller originally pointed out some of the pitfalls in this test but felt that nonstaining areas are often though not always cancerous. According to Martzloff's experience the overwhelming majority of unstained areas, including areas of leukoplakia, show no histologic evidence suggestive of probable beginning cancer. Small epithelial gland plugs, vermilion areas, a proportion of superficially situated nabothian follicle cysts, areas of epithelial loss, either when

superficial or, if complete, apparently when fibrin covers the base of the ulcer, epithelium involved in an underlying inflammatory process and particles of adherent inspissated secretion, together with other unexplained areas, fail to stain with the iodine. It follows that if areas that do not stain with iodine are not interpreted with due reserve they lead to endless confusion and alarm for the physician and unnecessary biopsy, cervical tinkering and hysteria for the patient.

The colposcope, since it facilitates visual observation of the cervix uteri, would naturally appear to answer a need. However, it has several drawbacks which probably will prevent its general adoption. These include the expense of the instrument, the time necessary to make a careful study and the need of extended experience to interpret correctly what one sees. The need of extended experience makes it necessary for the clinician to use the instrument regularly and to correlate the colposcopic appearance of the cervix with the histologic picture of the area in question. This requires frequent biopsies and study of the tissue by the clinician himself. The obtaining of tissue for biopsy takes the method out of the realm of simple office procedure. An adequate specimen for biopsy is probably worse than none, for it frequently makes it impossible for the pathologist to arrive at a correct interpretation. So far, the author has discovered with it neither areas of unmistakable probable beginning cancer nor any small cancerous ulcers (established cancer) which he could not detect with the unaided eye on careful methodical examination. It is important to appreciate fully that the gross appearance of the small lesion of early established cancer is not sufficiently characteristic to permit its differentiation from other nonmalignant

nant lesions solely on the basis of its appearance through the colposcope.

Malignancy and Radiosensitivity—

The radiosensitivity of carcinoma of the cervix is a relative feature, important in the therapy of this disease according to H. H. Bowing and R. E. Fricke.⁶ The radium technic employed at the clinic in the treatment of carcinoma of the uterine cervix may be defined as an intensive, multiple or broken-dose method. This procedure is orderly, flexible and effective. The radium therapist should have at his disposal an assortment of applicators such as universal tubes, various needles and gold (radon) seeds. The treatment factors, that is, the amount of radium, the filtration and the distance as a rule should remain constant, while the time of application and the interval between applications should be varied to meet the needs of the patient. Nearly all patients are placed in the knee-chest position in order to permit careful inspection and the introduction of applicators without trauma. The intervals are necessary to determine the radiosensitivity of the treated lesion. In cases in which such complications as tumor necrosis, local cellulitis, ulceration of the vaginal walls that is indicative of potential fistulas, or myometritis are present the intervals permit the proper institution of active measures to combat these serious, if not dangerous, conditions. In the final part of the course, the treatments are applied more rapidly. The radium therapy is followed by a course of so-called high voltage roentgen therapy.

If carcinoma of the uterine cervix and the associated inflammatory and degenerative process are effectively treated with radium and supportive measures, the result of treatment is prompt and its duration is evidenced by the percentage of 3-year cures. An attempt has

been made to use the late results as an index of the radiosensitivity of the lesion. Patients possess many potentialities which affect the results of irradiation. The immediate result is influenced definitely by the extent of the malignant process. The age and general health of the patient, the equipment and the skill and experience of the therapeutic radiologist have a definite influence on the late result. The best results are obtained in cases in which the treatment is classed as complete at the first session. However, subsequent treatment may produce relief that will last for years. The initial course of radium treatment requiring 2, 3 or more weeks is necessary before one can evaluate the immediate results and determine the radiosensitivity of the lesion. An interval of 3 months should elapse before one attempts to evaluate the late results.

At the Memorial Hospital, Healy reports 3500 cases of cancer of the cervix uteri, and is impressed by the advantages of giving x-ray therapy with the high voltage x-ray apparatus, 200 kilovolts, before radium is used. The technic of radium therapy has improved with the passing of the years. Of the patients treated in the early years by Bowing and Fricke, 14.4 per cent lived 3 years, but of the patients treated in the last 5 years of this study 42.7 per cent lived 3 years. Evidently the improvement in technic favored or enhanced radiosensitivity. Adequate radium therapy is not possible in all cases, and as a result patients do not all obtain the same response. In this study 565 traced patients received a complete radium treatment and 52.9 per cent of these patients lived 3 years. Only a limited radium treatment was possible in 739 of the cases in which the patients could be traced; 21.4 per cent of the patients lived 3 years. Evidently the adequacy

of treatment influences the radiosensitivity. The results according to age groupings are of great interest. Of the 458 traced patients who were between the ages of 40 and 49 years, 31.6 per cent lived 3 years; and of the 416 traced patients between 50 and 59 years of age 38.5 per cent lived 3 years. Evidently the older patients survive longer than do younger patients or radiosensitivity is influenced by the age of the patient.

Conization of the Cervix

The 899 electrosurgical conizations of the cervix performed at the University of Michigan Hospital during the last 4 years are discussed by N. F. Miller and O. E. Todd.⁷ The patient is hospitalized for 3 or 4 days. When the cutting current is properly combined with coagulation, the operation becomes a bloodless procedure and in this respect is in striking contrast to most cervical amputations, particularly the Sturmdorf operation. It takes about 6 weeks for complete epithelization to occur following conization. Stricture is prevented by placing an iodoform wick in the cervical canal at the time of operation in all patients except those who are to have a subtotal hysterectomy. This wick is removed on the third day and the patient is discharged with instructions to take a daily cleansing douche and report twice a week for check-up examination.

At this time the cervix is painted with an antiseptic, and a sterile sound or a hemostat is passed into the canal. This procedure is repeated at intervals of 2 weeks until epithelization is complete.

The authors believe that conization is indicated in (a) the correction of minor cervical disease and the prevention of remote complications of the cervix, in patients for whom subtotal hysterectomy is planned, (b) the eradication of deep-seated, chronic infections of the cervical

canal in older women, (c) for any condition of the cervix for which the Sturmdorf operation is indicated, (d) for obtaining adequate biopsy material in cases in which original biopsy material presented cytologic abnormalities strongly suggesting neoplastic change, and (e) as a substitute for older methods of trachelorrhaphy in most women, but especially in elderly women.

No serious immediate complication occurred in any of the 899 conizations. During the first few days there is little discharge and no discomfort but on the third or fourth day the discharge becomes profuse and is often bloody. Normally this serosanguineous or bloody discharge persists for 2 weeks, after which it gradually decreases. Vaginal cleansing douches are essential during this period of healing. Ultimate healing with complete epithelization renders the cervix clean and normal in appearance.

In a few patients small areas of delayed epithelization are noted. In these, healing may be hastened by the use of the fine nasal tip cautery. As strictures do occur (6.46 positive and 2.51 per cent probable), some of them severe, this warrants care in the selection of patients for conization and careful observation afterward.

Leukoplakia, Leukokeratosis and Carcinoma

W. Schiller⁸ emphasizes the fact that the term leukoplakia does not describe a definite and specific disease and that it presents neither a definite clinical entity, nor a well-defined pathologic, anatomic, or histologic picture. The word "leukoplakia" does nothing but convey the optic impression which the examiner gets either with the naked eye, or by means of a colposcopic examination; it describes a bright white patch. However, various changes of the mucous mem-

branes lead to the formation of similar white patches. It is impossible to determine with the naked eye, or even with magnifying instruments, the type of pathologic changes which underlie the leukoplakia.

We still know very little about the precursors of portion carcinoma. According to the authors' investigations, neither erosions nor inflammations form a basis for the development of carcinoma, but even the leukokeratosis and the abnormal proliferation need not be regarded as precursors of portion carcinoma.

CONTRACEPTION

L. Dewees and G. W. Beebe⁹ report on their experience over the past 12 years with contraception in private practice. A total of 884 white patients were investigated. Ninety-four per cent have been taught the diaphragm and jelly method. Analysis of the experience of the 662 patients who have been followed up indicates that:

1. The acceptance rate of the diaphragm and jelly method was 83 per cent—high enough to justify its routine prescription in private practice and low enough to illustrate the need for other prescriptions to a significant minority.

The chance of unplanned pregnancy, while relying wholly or partly on diaphragm and jelly, may be stated as 6 pregnancies per 100 woman-years of exposure for this group. This rate represents a reduction of from 93 to 96 per cent in the risk of pregnancy incurred by women habitually practicing no contraception.

Half of the 86 unplanned pregnancies followed errors or omissions that might account for conception.

The successful use of diaphragm and jelly did not retard conception after the method had been set aside for planned

conception. The time required for conception was reported for 136 of the 167 pregnancies known to have been planned. Half were conceived within 1 month and three-fourths within 3 months.

ENDOMETRIOSIS

Treatment—D. Dougal¹⁰ discusses the problem of the treatment of endometriosis. When the lesions are extensive, this must be radical and either *surgical* or *radiologic*. Dougal has very little experience with radiologic treatment and prefers to remove the uterus, preferably by *total hysterectomy* together with both appendages. It is necessary and, in fact, dangerous to dissect out growths from the bowel wall, as these will retrogress after the ovaries have been removed.

In less severe cases and particularly in younger women, treatment should, if possible, be conservative, but it must be realized that this may only relieve the symptoms for a time and have to be followed at a later date by a more radical operation.

It should be possible to reduce the incidence of external endometriosis by treating conditions such as subinvolution, backward displacements of the uterus, and uterine fibroids, which may predispose to retrograde menstruation, and by carrying out the various intra-uterine diagnostic and operative procedures at a time and in a manner least likely to drive fragments of endometrium into and through the fallopian tubes.

An interesting phase pointed out by the author is that the present-day custom of advising girls to lead a normal and active life during the menstrual period is open to objection for the same reasons, and it is quite possible that some of the pelvic endometriosis met with today is due to woman's emancipation and her

determination to ignore or minimize the handicap of the menstrual function.

Dougal doubts if shelling out of so-called tarry cysts of the ovary is ever possible, as a true endometriosis eats away the substance of the ovary and cannot be enucleated.

Conservative treatment of this kind is only possible if a correct diagnosis is made early in the course of the disease, and this necessitates a proper appreciation of the importance of such symptoms as acquired or increasing dysmenorrhea, particularly if associated with menstrual irregularity, pain in the vagina or on defecation, and high dyspareunia.

Recognition of the characteristic physical signs is equally important, and the earliest of these is either some diminished mobility or some asymmetry of the uterus. The presence of a nodular swelling behind the cervix is usually conclusive evidence of endometriosis in that situation, but occasionally small fibroids adherent in the pouch of Douglas may confuse the diagnosis.

Dysmenorrhea or dyspareunia of recent origin should always arouse a suspicion of endometriosis, and in the absence of well-marked physical signs be sufficient to warrant a careful examination under anesthesia or even an exploratory abdominal operation.

A clinical and surgical review of this subject is presented by V. S. Counseller.¹⁶ Endometriosis is an extremely important disease of young women, and its most predominant symptom is dysmenorrhea of an acquired or progressive type. Vesical and rectal pain superimposed on dysmenorrhea is almost always diagnostic. Diffuse pelvic soreness, brought about by walking or jarring of the pelvis in any way, is also suggestive.

It is definitely established that the syndrome produced by endometriosis is dependent on ovarian function. A rather

general rule can therefore be stated that removal of ovarian function will cause these lesions to become quiescent and in some instances to disappear. A few exceptions might be made, however, in the case of adenomyomas of the uterus following the menopause. Other factors producing activity of such adenomyomas may be accounted for by malignant ovarian tissue.

Since in most cases endometriosis occurs during the reproductive period, conservative surgical principles with regard to preservation of either the menstrual or reproductive function, or both, must be employed. Counseller believes that the upper age limit for conservative procedures is between 37 and 40 years. However, the extent of the lesions and their location are of more importance in selecting the type of operation perhaps than is the age of the patient. For example, if a patient at the age of 30 has a diffuse endometriosis involving the sigmoid, both adnexa and the uterus, she will be better off if a radical operation is performed.

It has been his observation that when it is necessary to perform radical hysterectomy for endometriosis before the menopause, the patients do not experience the severe menopausal symptoms that those patients do who undergo a similar operation for conditions other than endometriosis.

Conservative methods carry a more favorable prognosis when lesions are confined to the adnexa on one side and to a few serosal implants which can be easily excised. In younger patients with a longer history of dysmenorrhea and in whom endometriosis is encountered at operation he has in addition to conservative treatment performed presacral resection with the idea in mind that if there were recurrences the patients might not experience the dysmenorrhea which

was the original predominating symptom. By this means such patients might carry on in comparative comfort until later in life or until further symptoms justified destruction of ovarian function by surgical means or by irradiation.

In his combined series of 884 cases, 162 patients were treated by conservative procedures, 701 by radical procedures, and a few by radium and roentgen rays. When the lesions were diffuse, and particularly when there was considerable fixation of the lower uterine segment, even though the adnexa were not extensively involved, it was his opinion that the risk of recurrence following any conservative procedure was too great. Those patients who had involvement of the rectovaginal septum were treated in the great majority of instances by radium, because the surgical risk of excising this particular lesion is too high when it is considered that such patients can be treated satisfactorily by destroying ovarian function by radium.

Of the total of 162 conservative surgical procedures in addition to local excision, a tubal operation was employed in 9 cases, oophorectomy alone in 19, salpingo-oophorectomy in 51, local excision in 77, and bowel resection in 6, with or without uterine suspension and with or without presacral resection. Myomectomy was performed in 26 cases. This group of 162 patients comprises only 18.4 per cent of the total, which indicates that he has been more radical in surgical management of the disease than is shown by the report of previous authors. The selection of cases for conservative management, however, seems justified by the fact that he has had only a small number in which it was necessary to submit the patients to secondary surgical procedures or to radium therapy. Further justification lies in the fact that patients who have already undergone

previous pelvic operations, of which there were 167, were unwilling to assume the risk of recurrence. The average age of the group of patients treated conservatively was 33.8 years.

The question of fertility in endometriosis is of considerable importance. If the disease has existed over a long period, and if the symptoms are severe, the possibility of subsequent pregnancy should be quite remote. In the cases of these patients with secondary sterility, the onset of the disease frequently dates back a short time subsequent to delivery, giving cause to believe that the pregnancy or delivery may have been an exciting factor in its production or that the pregnancy or delivery may have reactivated a pre-existing endometriosis.

Thirty-one of 162 patients treated conservatively were unmarried, 131 were married. The figures for fertility are accordingly based on these 131 patients in whom one could expect pregnancy under normal conditions. In this group there was no pregnancy, or an absolute sterility, in 42 cases, or 32.1 per cent; 18 patients, or 3.7 per cent, had 1 live birth; 34, or 26 per cent, had 2 or more living births, and 22, or 16.8 per cent, had only miscarriages. The author was unable to obtain information in 15 cases, or 11.4 per cent. The incidence of pregnancy, therefore, for this group was 56.5 per cent. The incidence of miscarriage was extremely high, which is presumptive evidence that endometriosis is a very potent factor in it.

Seven patients were known to have become pregnant after such conservative treatment. Of these, 4 had 1 child each, 1 had 2 children, 1 had 4 children, and 1 had a miscarriage, giving a total of 10 children. It should be noted, however, that of the 162 patients who were treated conservatively, 64 were not traced in respect to subsequent pregnancies, 10

were more than 40 years of age at the time of operation, 18 were unmarried, and 15 were sterilized by operation, so that in only about 55 cases could one reasonably expect a report of pregnancy.

In order to alleviate the dysmenorrhea, the author has in addition to local excision been performing presacral resection. This latter was carried out in 13 of the cases in which local excision was performed. In 5 cases in which unilateral oophorectomy, and in one case in which bilateral salpingectomy was performed, a presacral resection was also carried out.

With regard to pain, approximately 70 per cent of the patients received sufficient relief, so that it was not necessary to subject them to subsequent treatment.

In the remaining 143 cases of this group of 162, presacral resection was not performed. Eighty-five of these patients were traced. Sixteen obtained moderate improvement (Grade 1 to 2), whereas 48 obtained practically complete relief from pain (Grade 3 to 4).

Approximately 75 per cent, therefore, were relieved of the pain for which they sought treatment. Twenty patients in this group were unimproved. In 7 of the cases it was necessary to apply subsequent treatment; in 1 case secondary oophorectomy and freeing of adhesions were carried out, and in 3 cases pan-hysterectomy was performed. Ovarian function was terminated by the use of radium in 1 case, and in 2 cases in which secondary pelvic inflammatory infection was suspected roentgen therapy was employed. One patient of the series died of peritonitis secondary to partial removal of an endometrial growth constricting the sigmoid. It is interesting to note that all the patients whom it was necessary to treat subsequently by irradiation or surgery were in this group in which presacral resection was not carried out. This in a way substantiates our

belief that presacral resection may be of considerable value in preventing later surgical treatment even though lesions may recur.

It is not possible to show that conservative procedures for sterility are of much value since only 7 of the 55 patients whom one could reasonably expect to become pregnant did subsequently become so. It seems to us that pregnancy can be expected only in those cases in which the disease is limited to 1 adnexa or to a relatively few implants which can be excised.

FALLOPIAN TUBES

Contractility

S. H. Geist, U. J. Salmon and M. Mintz¹² discuss the effect of estrogenic hormone upon the contractility of the fallopian tubes. They find that after the menopause, with the gradual cessation of the production of estrogenic hormone, there is marked impairment of tone of the musculature of the fallopian tubes and gradual disappearance of the regular rhythmic tubal peristalsis. This is demonstrated clearly in kymographic records by the reduced resistance to the entry of the gas and by the disappearance of regular rhythmic contraction waves. The most striking impairment of motility was observed in the cases longest after the menopause. In the recent cases, evidence of residual ovarian function was manifested by irregular contraction waves of low amplitude at low pressure.

Coincident with the impairment in tubal contractility, the vaginal smears exhibit signs of various degrees of estrogenic hormone deficiency. The most marked deficiency was observed in the patients showing least tubal activity.

Administration of estrogenic hormone in the form of the estradiol-benzoate (progynon-B) resulted in the develop-

ment of rhythmic contraction waves of high amplitude, similar to those observed in normal females with functioning ovaries.

Coincident with the reappearance of tubal contractions, the vaginal smears showed full estrogen effects.

The striking restoration of regular tubal contractions in these cases parallel with the marked estrogenic effect manifested in the vaginal smears following the administration of the estradiol-benzoate indicates that in the human female the ovarian estrogenic hormone is responsible for the production of the normal rhythmic tubal contractions. Furthermore, one must consider the possibility that impairment of tubal contractility due to estrogen deficiency may play a rôle in some forms of sterility and tubal pregnancy.

Ectopic Pregnancy

The relationship of fertility and sterility after extrauterine pregnancy is studied by C. W. Mayo and E. O. Strassmann¹¹. In the 10-year period from January 1, 1926, to December 31, 1935, 142 patients with ectopic pregnancies were seen at the Mayo Clinic. There were 140 tubal pregnancies, 1 ovarian pregnancy, and 1 abdominal pregnancy. 141 of the patients were operated on without a death, the remaining patient having come to the clinic in shock and having died before any surgical procedure could be attempted. The surgical mortality was therefore 0.0 per cent, the total mortality, 0.7 per cent.

In 77 cases (55 per cent) the tubal pregnancies occurred on the right side, in 63 (45 per cent) on the left. The higher percentage of right tubal pregnancies can be explained on pathological (former inflammations and operations on the appendix) and on mechanical grounds.

Forty-two of the 142 patients (29.6 per cent) could not have been expected to have subsequent pregnancies for various reasons. These patients were practically sterile or became sterilized after the ectopic pregnancy. Three of these patients had recurrent ectopic pregnancies when they first came to the clinic.

One hundred of the 142 patients (70.4 per cent) had the possibility of further pregnancy, at least theoretically. Eighty-four of them were traced, and 31 (36.9 per cent) became pregnant later, 28 (33.3 per cent) having intrauterine pregnancies, and 3 (3.6 per cent) having recurrent extrauterine pregnancies.

These 28 patients had 47 intrauterine pregnancies, 32 of which resulted in full-time deliveries with 29 living children; the others resulted in miscarriages and premature deliveries. Twenty-one full-time pregnancies occurred in 14 patients after salpingectomy, both ovaries being preserved; 11 full-time pregnancies occurred in 7 patients after salpingo-oophorectomy, 1 ovary being preserved.

From a review of the literature it was found that recurrent ectopic pregnancies occur in about 3.9 per cent of cases of ectopic pregnancy. Considering only those patients who have the possibility of subsequent pregnancy after their first ectopic pregnancy, one would expect this percentage to be higher. In their series of 84 patients who had had their first ectopic pregnancy treated at the clinic and who had the possibility of further pregnancy, the percentage was somewhat lower (3.6 per cent). The number of recurrent ectopic pregnancies occurring in a total of 142 patients (including those who had their first ectopic pregnancy treated elsewhere) was 4.0.

Since the probability of intrauterine pregnancy after 1 ectopic pregnancy is about 10 times larger than the probability of another ectopic pregnancy, conserva-

tive surgery is advisable in order to preserve fertility. Only if the other tube is severely diseased should it be removed. In this connection it should be kept in mind that the nonpregnant tube undergoes certain acute changes in more than 50 per cent of tubal pregnancies, such as swelling, redness, and peritoneal friction produced by hematomas. These changes, however, more or less disappear and do not interfere with subsequent fertility.

Tubal Insufflation

Reopening of tubes that have been ligated surgically to effect sterilization by uterine insufflation with carbon dioxide is reported by I. C. Rubin¹⁴

As to the manner in which insufflation opens up ligated tubes, it has been noted that whether the tubes are previously crushed, as in the Madlener operation, or not crushed, as in the Pomeroy method, the operations which are preferred by most surgeons, the pathologic change induced is localized at the point of ligation. Observations on the local condition following the operation are fairly uniform. A small fibrous band connects the severed end of the tubal loop, or fine adhesions bind them to adjacent viscera. The stricture, though complete, is limited to a very thin segment of the endosalpinx and tubal serosa in contrast to pathologic strictures, which as a rule occupy more extensive portions of the lumen of the tube.

As fallopian tubes that have been ligated were normal previous to the sterilizing operation, they remain normal except at the point of ligation. This renders the surgical stricture vulnerable to intratubal pressure.

Patency was re-established in 5 cases following ligation by pressure below 160 mm. of mercury. The operation of ligation had been performed by different

gynecologists. Apparently the more recent the ligation the less pressure is required to open up the tubes. Unless the interstitial portion of the tube has been resected, the artificially induced obstruction should yield to insufflation at a pressure of 200 mm. of mercury or less. In experienced hands the pressure level may be increased to 250 mm. of mercury. The latter, however, is recommended only as a therapeutic measure for the specific purpose of effecting a re-opening of ligated tubes. If the insufflation fails on the first trial to open the tubes, it can be conveniently repeated at suitable intervals. Should pregnancy not soon take place though tubal patency has been restored, the patient has the reassurance that the mechanical closure is no longer responsible for the sterility.

The flow of carbon dioxide is regulated at the rate of 1 cc. per second or slower, the pressure rise and pain reaction being observed if any are present. About 100 cc. of gas is adequate and the procedure requires from 2 to 3 minutes at the first trial.

Uterosalingography

A new medium for uterosalingography is presented by P. Titus, R. E. Tafel, R. H. McClellan and F. C. Messer¹⁵. Iodized oil injected into the uterine cavity and the fallopian tubes as the opaque medium for x-ray visualization is followed too frequently by sharp reactions, either from chemical irritation by the iodine, or allergic in type as though from the oils.

The foreign-body effects of iodized oil, persisting as this substance does for indefinite periods of time after injection into the abdominal cavity, result often in encysted masses with local acute and chronic peritonitis.

In an effort to avoid such reactions, a new nonirritating radiopaque com-

pound has been devised, consisting of mono-iodomethane sulfonate of sodium (skiodan) (40 per cent) with acacia (20 per cent).

This chemical compound does not release free iodine and is rapidly excreted from the body through the urine. The acacia, added for viscosity, does not have a foreign body effect as do poppy seed or sesame oils.

Adequate animal experiments were conducted to demonstrate, histologically and chemically, the correctness of the foregoing statements before beginning the clinical use of this medium with patients.

It has now been used in clinic on a series of patients over a period of nearly 2 years without clinical evidence of inflammatory or other reactions, either immediate or delayed. Moreover, the x-ray pictures appear to be more distinct than with the iodized oil preparations

GONORRHEA

R. Simons and C. A. Eindhoven¹⁶ employed an acridine derivative in the treatment of 18 women with gonorrhea. The preparation used by the authors was *flavadine*, an acridine preparation which contains arsenic in an organic combination and which, while not irritating like acridine hydrochloride, nevertheless has a good gonococcal action. The preparation was first used for the treatment of gonorrhea in 1932. Favorable reports about the preparation induced the authors to employ it in acute cases of gonorrhea, in preference to the new sulfanilamide preparation, which is better suited for the chronic cases.

Before treatment is instituted, cultures are made from material obtained from the urethra, cervix and rectum. In the treatment of the cervix uteri, the organ is exposed with the aid of a

speculum, the secretion is wiped away and then the flavadine is introduced by means of a syringe. At first 1 cc. is administered, then 2 cc. and then 3 cc. If some of the fluid flows back, it is wiped away to avoid erosions. For greater safety a tampon is introduced into the vagina; this can be removed by the patient on the following morning. The treatments are given daily for 8 days. After each series a control test is made. From 1 to 6 series are required for the treatment of cervical gonorrhea, but the average is about 3 series of 8 days each. In approximately half of the women treated, the cervix was cured after 8 days.

In rectal gonorrhea, in which flavadine was equally effective, 5 cc. was instilled and from 1 to 4 series of treatments were required for cure. The urethra was not treated with flavadine but rather with the usual silver preparations. The silver therapy required 1 or 2 months longer than the treatment with flavadine, but the cervix was never reinfected from the urethra. Reviewing the results of the flavadine treatment, the authors say that all 18 women were cured. Control examinations extending over periods of from 3 to 12 months proved that there was only 1 relapse, which actually may have been a reinfection. On the basis of these observations the authors think that flavadine is the remedy of choice in the local treatment of gonorrhea in women.

Sulfanilamide—L. M. Randall, F. H. Krusen and E. G. Bannick¹⁷ believe that gonorrheal infections of the female genital tract should first be treated by the administration of *sulfanilamide* as a large percentage of patients will respond to this therapy alone. In intractable cases they recommend a combination treatment with sulfanilamide and artificial fever therapy.

Treatment is commenced by the administration of 60 grains (4 Gm.) of sulfanilamide on the first day; this is divided into 4 doses of 15 grains (1 Gm.) each. On the second and third days 80 grains (5.3 Gm.) are administered in 4 doses of 20 grains (1.3 Gm.) each. Beginning on the fourth day a daily dose of 40 to 60 grains (2.6 to 4 Gm.) is resumed. At the end of a week of treatment cultures are taken from the uterine cervix and urethra. If the cultures are negative, administration of the drug is continued and the cultures are repeated in 2 or 3 days. If they again are negative, administration of the drug is discontinued. Repeated cultures are then taken until 4 negative cultures have been obtained. One of these must be obtained immediately following the cessation of menstruation. If at the end of a week of treatment the cultures still are positive, the treatment should be continued. Should infection still be evident in the cultures at this time it is well to ascertain the concentration of the drug in the blood. If this concentration is found to be below 6 to 9 mg. per 100 cc., the dose of sulfanilamide is probably insufficient and will need to be increased. One must consider the fact that a higher concentration may be necessary for certain strains of *Neisseria gonorrhoeae* and therefore larger doses may be necessary in some cases.

INTERSEXUALITY AND MALE SEX HORMONE

Womack and Koch first reported in 1930 that a substance having properties of the male sex hormone was found in normal human female urine and in normal human pregnancy urine. It is most interesting that this androgenic substance is not only present in normal

human female urine, but that it is present in very nearly the same concentration that it is found in normal human male urine. Estrogenic substance (female sex hormone-like substance) is found in normal male urine. The concentration of estrogenic substance is relatively higher, however, in female urine than in male urine. Androgenic substance has been found in normal human placentas. These facts make the results of the experimental work of R. R. Green, M. W. Burrill and A. C. Ivy¹⁸ on rats of more than academic interest. Large amounts of androgenic substance injected into the mother rat have so influenced sexual development of the embryo that a masculinized female or an intersexed animal has resulted. It is conceivable, then, that an excess of androgenic substance circulating in the pregnant human female may so influence sexual differentiation of the embryo that a masculinized human female or an intersex results.

MENOPAUSE

Estrogenic and Gonadotropic Hormones—K. M. Murphy and C. F. Fluhmann¹⁹ report their studies of the blood of climacteric women for the presence of estrogenic and gonadotropic hormones, and a consideration of the possible relation of these findings to the symptoms of the climacteric period.

This study is based on the examination of 44 climacteric patients, of whom 20 were premenopausal and 24 postmenopausal. A total of 132 tests were made for the presence of estrogenic hormone in the blood of 36 of the 44 patients. Of these, 58 were from premenopausal and 74 from postmenopausal patients. It is remarkable that estrogen was found in all patients, with 3 exceptions, both premenopausal and

postmenopausal The most frequent observation was a cyclic occurrence of the hormone, and it appeared in 15 of the 15 premenopausal women and in 13 of 21 postmenopausal patients. In the latter group 5 showed constant moderate amounts of estrogen, while in 3 the tests were consistently negative. On the other hand, it has not been possible to establish any relationship between the estrogenic content of the blood and the intensity of the patient's complaints.

The blood was examined for anterior pituitary gonadotropic hormone in 13 premenopausal and 15 postmenopausal women; a total of 70 tests were performed. An analysis of the results points to 2 important conclusions:

First, a much greater percentage of the postmenopausal women gave positive tests than those of the group still menstruating. Of 31 tests in premenopausal patients, 19, or 61 per cent, were negative and 12, or 39 per cent, were positive. In the postmenopausal group, 11, or 28 per cent, were negative and 28, or 72 per cent, showed the presence of gonadotropic hormone. Second, a definite relationship between the severity of symptoms and the occurrences of anterior lobe hormone could be established.

The authors draw attention to 2 observations: (a) The onset of the climacteric period is not associated with a disappearance of estrogenic substance, as determined by a sensitive laboratory test, and (b) there is a definite relationship between the onset and severity of vasomotor symptoms and the presence of increased gonadotropic hormone in the circulating blood.

Treatment — E. Novak²⁰ discusses the management of the menopause. It seems certain that endocrine imbalance, not only of the menopausal but also of other types, can occur at very different quantitative levels, so that it is futile to

lay down hard and fast rules as to the hormone dosage required. In many instances rather small doses of **estrogenic substance** seem to suffice; in others much larger doses are required. If for example, intramuscular injections of 2500 or 5000 international units of estrogenic substance in oil (such as **theelin**, **amniotin**, or **progynon-B**) do not give relief, the dosage may be increased to 10,000, 20,000 or rarely even 50,000 units. The heavier dosage, as a matter of fact, is the more popular plan in a good many of the European clinics, though certainly not always necessary.

The duration of treatment is likewise to be adapted to individual indications. Menopausal symptoms rarely are persistently troublesome, and it is usually only during exacerbations that active hypodermic medication is necessary, and only a few injections may be required. In the intervals the patient may need no medication, or at most the administration of some simple sedative of the bromide or barbituric acid group.

In other cases the oral administration of an active estrogenic preparation (amniotin, theelin, theelol, progynon-DH) may be necessary and, in fact, the milder forms of disturbance may require nothing more than oral treatment at any time. This is far more agreeable to the patient than hypodermic medication, and this method certainly is to be preferred when it seems to suffice.

In the severe type the hypodermic route is much more effective and prompt in its results.

By some such plan, or combination of plans, it has been possible to give varying but usually satisfactory relief in all but a very small proportion of cases. Occasionally the author has resorted to irradiation of the hypophysis, a method which has been highly vaunted in recent

years. Light hypophyseal irradiation is apparently harmless and may relieve the symptoms in some cases in which organotherapy has failed.

The value of the treatment of the menopause with purified or **crystalline estrogen** in 200 patients is presented by H. Wiesbader and R. Kurzrok.²¹ These patients were observed for not less than 6 months and, on the average, not more than 3 years. The etiologic factor in the causation of the menopause was spontaneous menopause in 160, surgical menopause in 34 and radiation menopause in 6. Some measure of relief was obtained in all subjects. The best results were obtained in the patients who had stopped menstruating completely. Patients who were menstruating regularly did not respond as well. The patients who were still menstruating reduced their flushes by two-thirds. On the contrary, a patient with complete menopause frequently reduced her flushes from 40 to 50 a day to from 1 or 2. Not only did the improvement manifest itself in the bettering of isolated symptoms, but there was often a marked improvement in the well-being of the patient. Irritability, sleeplessness and fatigue subsided rapidly. The arthritic changes arising at the menopause (except those due to focal infection) respond to therapy, but the response is not the same in all patients. Possibly the patients who responded only moderately to therapy suffered from a type of arthritis that was both infectious and metabolic in character.

In general it required the persistent injection of large doses of estrogens (50,000 international units) twice a week, over a period of 2 or more months, to obtain a good result in the responsive type of patients. Premenstrual depression was relieved in all except 1 patient. Patients suffering from migrainous head-

ache were definitely relieved. Uterine bleeding reappeared in those patients in whom menstruation had previously ceased. Examination of endometrial biopsies obtained at the time of bleeding showed a proliferative type of endometrium. The total dosage of estrogen which produced the bleeding varied greatly, ranging from 250,000 to 2,000,000 international units. All bleeding ceased when the injections were discontinued or the dose decreased. The menopausal symptoms were entirely relieved in some patients during such bleeding and made distinctly worse on others. Treatment should not begin before definite distressing menopausal symptoms appear. Similarly, treatment is continued until there is a tendency for the distressing symptoms to disappear. This varies according to the patient, it may range from 6 months to 3 or more years.

Postmenopausal Bleeding

The causes of postmenopausal bleeding from the cervix and uterus in 782 cases have been analyzed by F. E. Keene and F. S. Dunne.²² In more than 60 per cent the bleeding was due to malignancy.

In 78.4 per cent of the patients, bleeding was due to some form of neoplastic disease in the cervix, body of the uterus, or adnexae, and 75.4 per cent of these neoplasms were malignant.

The cervical lesions were neoplastic in 72.2 per cent; the fundal, in 84.5 per cent.

In the entire series the lesion responsible for the bleeding was of cervical origin in more than one-half of the cases, and 56 per cent of these lesions were malignant.

In 40 per cent of the cases, bleeding was due to lesions in the body of the

uterus, 61.5 per cent of which were malignant.

Adnexal lesions are not a common cause of postmenopausal bleeding; 64.5 per cent of the adnexal tumors were malignant.

In 38 cases no organic cause of the bleeding was demonstrable. In 13 of these, endometrial hyperplasia was present.

Postmenopausal bleeding—whether of cervical or fundal origin—is always of serious prognostic import, since in the majority of instances it is due to malignancy.

Given a normal cervix, approximately two-thirds of the lesions responsible for uterine bleeding after the menopause are malignant.

MENSTRUATION

Dysfunctional Menstrual Disorders

Treatment—The treatment of dysfunctional menstrual disorders should be directed toward the primary site of the derangement, usually the anterior hypophysis or the ovaries. The therapeutic agents currently advocated for these non-organic menstrual disorders are described by S. L. Israel.²³

1. **General Measures**—The importance of a proper diet to women of child-bearing age is amply established. **Vitamin A**, serving in some subtle fashion to increase the state of nutrition, is deemed vital to the underweight woman. An increased intake of protein benefits those women suffering from hypophyseal deficiencies. When either obesity or malnourishment is present, appropriate measures should be applied.

2. **Estrogen**—The use of ovarian follicular hormone, theelin or other estrogens is *contraindicated* in the treatment of any type of dysfunctional uterine hemorrhage. Since the cause of such

bleeding is usually a continued and unantagonized action of this very principle, its administration in such instances would be irrational, ineffective and probably harmful.

3. **Anterior Pituitary and Anterior Pituitary-like Preparations**—Extracts of the anterior hypophysis containing both gonadotropic hormones, the follicle-stimulating and the luteinizing factors, and preparations of pregnancy urine (prolan) containing only the latter have a wide field of application in dysfunctional menstrual disorders. The administration of the **luteinizing factor** (prolan or pituitary-like principle) is indicated in the dysfunctional uterine bleeding of puberty and childbearing age. The dysfunctional uterine bleeding of the menopause, being associated with sclerotic ovarian changes and independent of hypophyseal deficiency, should not be treated by this substance. From 65 to 80 per cent of patients under 40 are restored to temporary menstrual normality by intramuscular injections of 200 R. U. of the luteinizing principle, given daily during the bleeding phase and semiweekly for 6 to 8 weeks after the bleeding has ceased. However, in more than 50 per cent of those benefited, the bleeding recurs within 6 months because the primary disorder remains unaffected by this treatment. To avoid such recurrences, the concomitant administration of **low-dosage irradiation** to the **pituitary gland** and **ovaries** is advisable.

Irregular menstrual periodicity, often associated with bouts of uterine bleeding, and amenorrhea are more adequately treated by the simultaneous administration of both the anterior pituitary and the anterior pituitary-like hormones. The combination gives a much greater ovarian response in animals, and is more effective in the treatment of certain types of amenorrhea than either of the two sub-

stances employed individually. Two hundred rat units of the luteinizing factor (PU extract) and 2 cc. of whole anterior pituitary extract are administered intramuscularly 3 times weekly for 6 to 8 weeks. Such combined substitutive therapy is effective in 50 per cent of the patients with amenorrhea caused by pituitary deficiency, but of no avail in the amenorrhea of primary ovarian failure wherein an excess of pituitary sex hormone is already present.

4. **Thyroid Extract**—Desiccated thyroid extract is a most effective weapon in the treatment of dysfunctional menstrual disorders. Acting as a specific agent, thyroid extract promptly alleviates the menorrhagia of hypothyroidism which is often the cause of hemorrhages in adolescent girls. In such instances the B. M. R. may be only moderately lowered to a level between -10 and -20 per cent. Thyroid extract is also of value when employed empirically as a nonspecific adjuvant in therapy, because of its augmentation of all cellular activity. The toxicity of overdosage may be avoided by observing 2 principles of thyroid therapy: (a) The initial dose of desiccated thyroid extract should be small ($\frac{1}{4}$ grain or 0.016 Gm., t i d) irrespective of the B. M. R. The amount administered should be increased rapidly to the point of tolerance, and the maintenance dose continued at a slightly lower level. (b) The commercial varieties of desiccated thyroid contain different amounts of thyroxin. Thus, to insure accurate dosage for any given patient, the same brand of extract should always be specifically requested in renewal prescriptions.

5. **Low-dosage Irradiation**—Low-dosage irradiation of the pituitary gland and ovaries is one of the most valuable remedial agents in the treatment of both dysfunctional uterine bleeding and

amenorrhea. A favorable response in 50 per cent of the patients with amenorrhea and in 80 per cent of those with menometrorrhagia is reported. The proper technic includes 3 treatments at weekly intervals to both the pelvis (ovaries) and pituitary fossa. "In the patient of average size the technical factors are 127 Kv, 5 ma., 14-inch distance, 5 mm. aluminum filter for 3 to 5 minutes. This is equivalent to $7\frac{1}{2}$ to $12\frac{1}{2}$ per cent S. E. D. or 50 to 80 R." (Edeiken).

6. **Radium**—Intrauterine radium irradiation is of definite value in the treatment of dysfunctional uterine bleeding of the menopause. Intrauterine irradiation should not be employed, except as a last resort, in dysfunctional bleeding of the third and fourth decades. The amount of intrauterine irradiation, instituted immediately following the exploratory curettage, should approximate 1200 milligram-hours, a dose which will control almost all instances of dysfunctional hemorrhage. If the endometrium recovered is subsequently proved to be malignant, **total hysterectomy** is the procedure of choice.

7. **Venom**—Recently, the use of moccasin snake venom (*Ancistrodon piscivorus*) has attained a certain therapeutic vogue in various hemorrhagic conditions. The venom of individual moccasin snakes varies in activity and deteriorates with time. Therefore, it is best to employ dated, pooled venom obtained from a reliable source. The venom is employed in a 1:3000 dilution and given subcutaneously. The initial dose should be 0.5 cc. and subsequent injections increased rapidly to 1.0 cc. It should be given daily during episodes of bleeding and, when the hemorrhage has been controlled, 2 or 3 times weekly for 3 to 4 months. The severe local reactions manifest by certain individuals who are hypersensitive to the venom

may be avoided by a desensitization technic.

8. **Progestin**—Although progestin therapy is rational because it counterbalances the estrogen dominance which exists in dysfunctional bleeding, it is only a substitutive treatment and yields a temporary effect. It may be advisable to use progestin for the temporary arrest of the bleeding in conjunction with other agents employed to correct the basic ovarian or pituitary disturbance. The dosage of the crude corpus luteum extract (progestin) is still purely empiric. Rapid cessation of dysfunctional bleeding has been reported following the administration of 0.04 to 10 I. U. daily.

9. **Insulin**—The administration of insulin has been advocated in the treatment of dysfunctional menstrual disorders for more than a decade. Insulin seems to be most effective in the menstrual disorders associated with asthenia and malnutrition. Whether the insulin acts directly by stimulating the ovaries or indirectly by increasing appetite, weight and well-being is not clear. The customary dose of insulin recommended for nondiabetics is from 5 to 10 U before breakfast and supper.

10. **Surgery**—While the diagnostic value of uterine curettage is unquestioned in menstrual disorders, its use as a therapeutic measure is not often justifiable. Temporary relief from hemorrhage will be obtained following curettage because the bleeding surface is removed.

Mechanical dilatation of the cervix is sometimes of value in the treatment of gonadal deficiencies. It may be that increased ovarian activity follows cervical stimulation or dilatation in humans, as well as in animals.

Resection of the ovaries, more especially when they are palpably polycystic, is occasionally advocated as a treatment for dysfunctional menstrual disorders.

Any treatment requiring a laparotomy, however, should be relegated to that small group of women whose menstrual disturbances fail to respond to the single or combined use of other remedial agents.

Dysmenorrhea

C. F. Fluhmann²⁴ studied the hormonal activity in 19 women with severe dysmenorrhea. No pelvic or systemic cause for the painful menstruation was found. Eighty-five tests for estrogen were conducted by the mucification test; at least 3 on each patient were performed at weekly intervals. The blood estrogen of the 19 patients failed to demonstrate any consistent departure from the normal, either in the amount of estrogen present or in the type of curves obtained. In 11 instances a single peak in the concentration of the substance occurred during the interval and presumably was associated with ovulation. In 7 cases the interval rise was present, but a secondary increase also was noted at about the time of menstruation. The only abnormal observation was in a young woman of 19, in whom there was a definite increase of estrogen at the time of menstruation and no peak during the interval. The author objects to accepting any of the theories (deficiency of estrogen, excess of estrogen or deficiency of progestin and overactivity of progestin) which seek to explain the cause of primary dysmenorrhea solely as a hormone deficiency or excess.

Premenstrual Tension

This condition, only recently recognized as a pathological syndrome, is described by S. L. Israel.²⁵

When well marked, premenstrual tension is readily recognized. It occurs in women between the ages of 20 and 40 years and is characterized by a cyclic alteration of personality. This alteration

appears abruptly from 10 to 14 days prior to the expected menstruation and terminates dramatically with the onset of the flow. The monotonous periodicity of the syndrome and its precursive relationship to the menses are striking phenomena. The illness regularly begins as a dire and foreboding sensation of indescribable tension. There are marked physical unrest and constant irritability. The illness may mimic an oncoming mental disease when the more exhausting episodes of motor activity are followed by brief periods of depression and hebetude. Unreasonable emotional outbursts and causeless crying spells, similar to those which characterize the menopausal syndrome, are frequent. Persistent insomnia, vertigo, painful turgidity of the breasts and constant headache are frequent accompaniments of the syndrome.

The curious phenomenon of premenstrual ulcerative stomatitis, attributed to defective luteinization, may be one of the manifestations of premenstrual tension. Such women, according to Frank, do not excrete estrogen in a normal manner. During the premenstruum, the concentration of estrogen in the blood rises and affects the sympathetic nervous system to the extent of the symptoms produced.

It is suggested by Israel, however, that premenstrual tension is caused, not by an excess of circulating estrogen, but rather by the presence of unantagonized estrogen. This implies that the primary cause of premenstrual tension is deficient ovarian luteinization, with a decreased production of progesterin.

The 4 patients curetted just prior to or on the first day of a menstrual flow showed the phenomenon of pseudomenstruation, cyclic uterine bleeding, from an endometrium lacking the secretory influence of the corpus luteum hormone,

progesterin. Such an abnormality may be caused by deficient production of the anterior hypophyseal luteinizing factor or by a refractory state of the ovaries.

Treatment—Seven of the 10 patients who submitted to treatment were given 1 I. U. of **progesterone** intramuscularly daily or every other day during the second half of each menstrual cycle for from 2 to 3 months. Five of the 7 patients were entirely symptom free, and the remaining 2 noted considerable improvement during the period of treatment. In 6 patients the syndrome reappeared, however, immediately after withdrawal of treatment. The remaining patient, despite the lack of an adequate explanation, was free from premenstrual tension for 2 years after 3 courses of progesterone.

Seeking more permanent results, the author subsequently employed low dose **irradiation of the pituitary gland and ovaries** for 4 of the progesterone-treated patients and for 2 other patients who had received no previous treatment. The roentgen treatments included 3 treatments of from 50 to 80 R at weekly intervals to both the pelvic and the pituitary fields. In a patient of average size, the roentgen factors for each treatment are 127 Kv., 5 ma., 14-inch distance, 5 mm aluminum filter for 3 to 5 minutes (Edeiken). Four of the 6 patients so treated have remained free from premenstrual tension during observation periods varying from 1½ to 2½ years. The remaining 2 patients were also symptom free after the roentgen therapy, but they suffered recurrences of the syndrome after 6 months and 2 years, respectively. Both patients received second courses of low dose irradiation and have now been well for more than a year. The periodicity of the menstrual cycle was undisturbed in all the women treated by roentgen rays.

OVARIES

Ovulation

In relation to sterility the determination of the exact time of ovulation is important in that it will afford an opportunity to determine the optimum time for coitus or artificial insemination or to determine the biological attractiveness of an ovum to the semen of a mate. As far as contraception is concerned, the exact time of ovulation may lead to further advances of our knowledge of the fertile period

The determination of electrical characteristics of the living system has been speeded up by the development of a vacuum potentiometer to measure minute voltage changes in living systems. Through the use of this mechanism it is now possible to determine in experimental animals and human beings the external signs of ovulation. The work of Burr, Hill, and Allen in 1935 on the rabbit has been confirmed and extended to human beings to the extent that the time of rupture of the Graafian follicle may be very closely determined

In rabbits, Burr, Hill, and Allen detected by means of a vacuum tube potentiometer a marked difference of potential between a suprapubic and a vaginal electrode when each ovulation occurred. J. Reboul, H. B. Friedgood and H. Davis,²⁶ employing a similar technic, with the abdomen open and the ovaries under inspection, found that the peak of the potential difference was reached at about the moment of follicle rupture. Usually the potential difference passed through a maximum of 6 to 10 mv within 30 seconds and returned gradually to its former level in 5 to 25 minutes

H. S. Burr, L. K. Musselman, D. S. Barton and N. B. Kelly,²⁷ applying electrodes in the same places, obtained

marked changes in potential in a human female at the time when, as shown by subsequent laparotomy, ovulation could have occurred.

J. Rock, J. Reboul and J. M. Snodgrass²⁸ utilized women who needed laparotomy for a condition which did not entail any significant ovarian pathology or dysfunction, and made their observations between the seventeenth and eleventh days (inclusive) before any likely subsequent menstruation.

In 6 patients examination of the ovaries was made within 30 hours and in 1 case 51 hours after the electrical change. In another patient the curve of ovulation was not recognized until more than 8 days had elapsed. Operation then showed endometrial and corpus luteum development which, according to present standards, placed ovulation about 8 days before operation.

These experiments strongly indicate that associated with human ovulation there is a characteristic change in the electrical condition in the pelvis which has not been observed at other times in these cases, or at any time in subjects who have no ripe follicles. So far this change has been identified as an increase of the preceding and succeeding differences in potential between two pelvic electrodes

The curve suggesting ovulation occurred in all 9 cases during the time expected on the basis of current theories of ovulation time

The results of their experiments on the Ogino-Knaus concept for determining the time of ovulation are presented by J. E. Lackner, H. Wachtel and S. Soskin.²⁹ According to Knaus, the uterus of the normal woman manifests spontaneous, rhythmic contractions during the first 14 days of a 28- to 30-day menstrual cycle. During this portion of the cycle, the uterus responds with

increased contractions to the administration of posterior pituitary extract. Ovulation occurs on the fifteenth day. Twenty-four hours later the uterus has become flaccid and quiescent, and no longer responds to posterior pituitary extract. This corpus luteum phase lasts from the sixteenth day of the cycle until 48 hours before the ensuing menstruation. At this time the uterus reverts to the motility and responsiveness characteristic of the first 14 days of the cycle. If one can accept these findings of Knaus as correct, then one can believe him that it is possible to determine the date of ovulation with some degree of exactitude, by observing the day of the cycle upon which the uterus ceases to respond to the administration of pituitrin. It would thus be possible to establish the "safe period" for healthy women with regular menstrual periods providing the duration of viability of the sperm and ovum were known.

Lackner and his associates studied a number of the important aspects of the menstrual cycle throughout the cycle, in 15 normal women. The phenomena observed included the spontaneous motility of the uterus, uterine response to the administration of preparations of the posterior pituitary gland, changes in the uterine endometrium, and the urinary excretion of prolactin and estrin.

The outstanding observation made during this work has been the irregularity of the above phenomena in various normal women, and their unpredictability for any given normal woman. The number of exceptions was so great as to preclude the use of these phenomena as reliable criteria of normal sex function.

The results obtained from the administration of posterior pituitary preparations do not agree with those of Knaus from which he concluded that there was a single regular ovulation time for nor-

mal women. Normal women (in this country at least) ovulate at widely differing times in the menstrual cycle so that grave doubt is cast upon the Ogino-Knaus theory of the so-called "safe period."

The Cycloscope—J. Samuels,³⁰ of Amsterdam, Holland, also discusses an exact method of determining ovulation time and pregnancy by means of a cycloscope. This consists of a spectroscope, a lens, 2 rubber or metal cushions which press on the interdigital fold, stopping the circulation, each with an opening of 6 mm., a pair of forceps, and a light of about 150 candlepower (an ordinary show window lamp with a mercury mirror). The basis of the method is as follows: One of the interdigital webs, preferably that between the thumb and index finger, is clamped off by means of the fenestrated pelotte of the cycloscope, inducing a temporary interruption of the circulation, measuring about 6 mm. Spectroscopic examination of this section of the tissues in good illumination shows in the yellow and green portions of the spectrum 2 sharply defined dark absorption bands—those of oxyhemoglobin—between which is found a sharply defined light yellow band. After a short time the dark bands become indefinite, fade away and finally disappear. In the place of these bands, separated by an interval of yellow, there appears a broad, gray homogenous band. At this point reduction of the oxyhemoglobin has been completed. The tissue which is being examined has combined with the oxygen of the oxyhemoglobin (tissue respiration). The reduction time may be taken in 2 or 3 successive observations for accuracy and the average computed. After from 5 to 7 seconds, 2 new bands are to be seen, lying somewhat more closely to each other, *i. e.*, separated by a narrower yellow-green space. The

whole picture is less distinct and lies more to the left of the spectrum than the oxyhemoglobin bands. These are the absorption bands of methemoglobin. If conditions are further observed, it is seen that the methemoglobin bands again disappear with a rapidity which varies in different persons (from 10 to 40 seconds). This sequence of events is repeated several times at a quicker rate (tissue respiration). After the reduction time has been measured the constriction is released, so that circulation is restored and there is a sudden reappearance of the oxyhemoglobin bands with the broad yellow band in between. It is advisable when making successive counts not to clamp the same place each time.

Thus the cycle curve, the ovulation time and pregnancy can be determined. In normal subjects with a balanced endocrine system the reduction time is about 150 seconds. In a sexually mature woman these figures are apt to oscillate. If the reduction figure is ascertained every day for 1 month in a woman in the prime of her sexual life with a cycle duration of 28 days, such a cyclogram shows 3 declines, of which 1, the decline of menstruation, is most pronounced. The 2 other declines are shorter in duration and deviate slightly. In abdominal operations performed after the ovulation, decline had been observed with the aid of the cycloscope, a recently burst Graafian follicle was always seen. This method of examination has proved that a woman released at least 2 ova during 1 cycle. By the use of the cycloscope the day on which a woman ovulates can be determined accurately. In the cyclogram the menstruation decline, the first highest preovular position, the first ovulation decline, the second highest preovular position, the second ovulation decline and the highest premenstrual position are recognized.

In pregnancy the cycle oscillations cease. Therefore pregnancy can be diagnosed, since the daily reduction figures always remain constant. In case of an early pregnancy in a healthy woman with a balanced endocrine system, daily constant reduction figures of from 155 (youthful gravid women) to 165 are found. From the second till the seventh or eighth month this figure is constantly around 160, rising toward the end of the pregnancy to 155. Shortly before delivery these figures drop to around 165, often showing oscillations immediately before the birth of the child. By this simple method the differential diagnosis between fibromyoma and pregnancy can easily be made.

According to J. Samuels,³¹ a sexually mature woman ovulates twice in each cycle, young nulliparas 3 times. The ripening of the second ovum suppresses the formation of the corpus luteum of the first ovum by means of hormone. Nidation takes place within 3 days after fertilization, as all early pregnancy cyclograms indicate. The surface cells of the endometrium die to the accompaniment of bleeding when there is a sudden change or withdrawal of hormone. These cells usually die as a result of the withdrawal of luteal hormone, but it is certain that a sudden cessation of the supply of folliculin can also cause this.

Bleeding may also occur in the case of young girls during an ovulation as the result of a sudden and sharp decline in the curve. It may also occur when large quantities of folliculin are supplied to the endometrium and then suddenly withdrawn. A corpus luteum and luteal hormone are not essential to desquamation with bleeding. When the hormone changes are slow the endometrium can recover without bleeding. The mucous membrane is transformed by the second corpus luteum menstruale.

Cyclograms tend to prove that in all probability predominating luteinizing hormone of the hypophysis may also incite the first suppressed corpus luteum to form luteal hormone after the second unfertilized ovum had died. The possibility of fertilization is greatest during the ovulation decline and the 2 to 3 days preceding it. On the third day after the beginning of the ovulation decline the possibility of fertilization is only slight; thereafter fertilization is impossible. A woman is absolutely sterile for 3 days after the second ovulation decline until from 2 to 3 days after menstruation begins. After this she is relatively sterile until 3 days before the first ovulation decline. The cyclogram accordingly serves as a guide in determining all processes of ovulation and conception and in diagnosing and treating irregularities of menstruation. The cycloscope will therefore prove to be an indispensable instrument not only for the gynecologist but also for all general practitioners.

R. Imbach,¹² of the woman's clinic in Zurich made his studies with the cycloscope recommended by Samuels. In a considerable number of women between 21 and 45 years of age and in 1 man, the reduction time was determined daily over a period of 75 days.

As recommended by Samuels, curves were plotted of the reduction time in order to obtain so-called cyclograms. It was found that the technic is not as simple as had been suggested by Samuels and that there are many sources of error, for instance, it was found that the reduction time differs after the hands have been bathed in warm or cold water. Moreover, there is a difference whether a thick or a thin fold of skin is clamped off.

The results obtained by the author do not tally with those obtained by Sam-

uels. In not a single one of the normal persons subjected to the cycloscope test did he obtain curves that approximated those of Samuels. He reaches the conclusion that Samuels' spectroscopic method does not reveal typical increases and decreases in the reduction time of the oxyhemoglobin within the monthly cycle and that the far-reaching and revolutionizing conclusions arrived at by Samuels lack a foundation that stands up under investigation.

Experimental Production of Ovulation — Ovulation in the human is probably the result of a proper balancing of prolans A and prolans B. It has been a relatively simple procedure to produce ovulation experimentally in most laboratory animals. However, attempts to reproduce this phenomenon artificially in the human female have met with no success. This is probably due to the fact that specific gonadotropic hormones have not been isolated in a sufficiently pure state. Extracts of the anterior lobe of the pituitary gland which, theoretically, should be the ideal substances, have not been available in a sufficient state of purity for human therapy.

M. E. Davis and A. K. Kott,¹³ report on the experimental production of ovulation in the human subject with pregnancy mares' serum. For a limited period the blood of pregnant mares contains a high concentration of a gonadotropic substance. This substance reaches its maximum concentration about the seventieth day of the animal's gestation. At no time does it appear in the urine.

A highly purified preparation of this gonad-stimulating substance has been obtained. These hormone fractions are obtained as dry, white, water-soluble powders which are remarkably stable, furnishing a satisfactory basis for preparing sterile solutions for laboratory and clinical studies. It has been biologi-

cally assayed by a method developed in the laboratories which is based upon the increased weight of the ovaries of immature female rats injected with hormone as compared with those of uninjected controls. The rat unit has been defined as the total dose of hormone which, given in divided daily subcutaneous doses in 21- to 23-day-old female rats weighing 30 to 40 Gm, will produce by the fifth day a pair of ovaries weighing 65 mg, which is 5 times the weight of the ovaries in the uninjected controls.

In their earlier experiments the authors administered the fraction both subcutaneously and intramuscularly with varying results. Previous experimental work indicated to them that the use of this substance was likely to be most successful when administered intravenously. The available patients were carefully tested for protein sensitization, and the hormone was then administered intravenously. Women who were to be subjected to laparotomy for a variety of pathologic conditions were chosen for this work.

Recent ovulation was present in approximately half of the patients to whom this substance was administered. To make certain that an ovulation is of recent origin, it is almost always necessary to obtain histologic sections of the corpus luteum.

Most of the patients received about 60 units in a single dose. The authors believe that this substance is capable of causing rapid follicle growth, and that these follicles rupture, release their ova and are converted into corpora lutea all within the space of 24 to 36 hours. The therapy of this new gonadotropic material, therefore, involves the treatment of patients in whom ovarian failure has resulted in a lack of follicle development and an absence of normal ovula-

tion with their concomitant menstrual abnormalities or infertility.

Much laboratory experimentation indicates that the amount of hormone sufficient to stimulate growth of follicles may not be sufficient to produce ovulation. Too large an amount of gonadotropic substance causes the formation of many atretic follicles and the imprisonment of their ova but no ovulation. The authors have some clinical evidence that the most effective mode of administration is to give 2 or 3 intramuscular injections of 15 or 20 units at daily intervals to be followed by a single intravenous administration of the same or a larger amount. Thus, follicles can be stimulated to grow to maturity at which stage the intravenous administration provides the stimulus necessary to cause ovulation.

Tumors of the Ovaries

V. S. Counseller and A. C. Broders^{3,4} propose a working classification of adnexal cysts and neoplasms. This is based not so much on the histologic nature of the tumor as on the rate and manner of growth of the tumor and what it does to the patient. The term "papillary" in this classification indicates malignancy. It is pathologically sound to regard and to treat as malignant any tumor which results in the formation of papillary epithelium, particularly if the growth tends to perforate the primary wall and to implant itself on adjacent structures.

ANATOMICOPATHOLOGIC CLASSIFICATION OF ADNEXAL CYSTS AND NEOPLASMS

I. Ovaries

A. Cysts

- 1 Inflammatory (subserosal)
- 2 Simple
 - (a) Unilocular
 - (b) Multilocular
- 3 Cysts of corpus luteum
- 4 Dermoid cysts (benign)

B. Neoplasms:**1. Benign:**

- (a) Cystadenoma
 - (1) Unilocular
 - (2) Multilocular
- (b) Adenomyoma (endometriosis)
- (c) Fibroma
- (d) Leiomyoma (fibromyoma)
- (e) Luteoma

2. Malignant

- (a) Papillary adenocarcinoma
 - (b) Carcinomatous cystadenoma
 - (1) Papillary
 - (2) Nonpapillary
 - (3) Mixed
 - (c) Solid carcinoma
 - (d) Carcinomatous dermoids
 - (e) Luteoma
 - (f) Teratoma
 - (g) Sarcoma
 - (h) Secondary carcinoma
- 3 Neoplasms of questionable nature**
- (a) Granulosa cell tumor
 - (b) Arrhenoblastoma

II Parovarium

- .1 Cysts
 - 1 Unilocular
 - 2 Multilocular
- B Neoplasms
 - 1 Leiomyoma

III Fallopian tubes

- .4 Cysts
 - 1 Hydatids of Morgagni
- B Neoplasms
 - 1 Benign
 - (a) Adenomyoma
 - 2 Malignant
 - (a) Adenocarcinoma
 - (b) Squamous cell carcinoma
 - (c) Secondary carcinoma
 - (d) Sarcoma (rare)

Disgerminoma - The 4 malignant ovarian tumor types which have come to be spoken of as "special ovarian tumors" offer a far more favorable prognosis than does ovarian cancer in general. In this group belong (a) granulosa cell carcinoma, (b) arrhenoblastoma, (c) disgerminoma, and (d) the so-called Brenner tumor. The first 3 tumor types are unquestionably to be classed as malignant on both clinical and histologic grounds.

In its earliest stages the anlage of the gonad is a collection of cells on the an-

terior or ventral surface of the Wolffian body, cells which in this undifferentiated phase of gonadal development possess neither male nor female attributes, for the spark of sex has not yet been applied. Once this spark has been applied, the sex direction of gonadal development is determined along ovarian or testicular lines, as the case may be. Tumors arising from gonadogenic elements in this differentiated phase of the sex gland area may develop in later life, producing the feminizing granulosa cell carcinoma or the masculinizing arrhenoblastoma.

E. Novak and L. A. Gray³⁵ discuss a clinical and pathological study of 17 cases of disgerminoma of the ovary. This tumor probably arises from cells which date back to the undifferentiated stage of gonadal development before its cells have become tinctured with either female or male attributes.

Disgerminoma is pre-eminently a tumor of early life. It is common in children before puberty, and likewise in young adolescents. The size of disgerminomas varies between wide limits, some measuring only a few centimeters in diameter, others being so large as to fill the abdominal cavity.

There are few tumors of the ovary which present such distinctive histologic characteristics as does disgerminoma. This applied to both the cell type and the general architecture of the tumor. For this reason the microscopic recognition usually is very easy, once one has familiarized oneself with the microscopic criteria. The large round, ovoid or polygonal cells of disgerminoma are responsible for the former designation of this tumor as the "large-cell carcinoma" (grosszelliges Karzinom). The cytoplasm is abundant, clear, very pale-staining and often translucent. The nucleus likewise is large, round and stains heavily with hematoxylin. Mitotic fig-

ures are seen in varying number, though not usually numerous.

Just as characteristic is the arrangement of the cells in alveoli of nests separated by septa of fibrous tissue which shows more or less hyalinization, and white quite constantly shows extensive lymphocytic infiltration.

Disgerminoma exhibits no endocrine activity, being made up of sexually indifferent cells. In this respect it differs from the feminizing granulosa cell carcinoma and the masculinizing arrhenoblastoma. Disgerminoma is often observed in sexually underdeveloped or pseudohermaphroditic individuals, but it has nothing to do with the production of these sex abnormalities, which persist even after removal of the tumor.

While disgerminoma is undoubtedly a malignant type of tumor, there are marked variations in the degree of malignancy of individual tumors. The outlook is very favorable when the tumor is unilateral, with intact capsule. The results are much less favorable when the capsule has been broken through, with extensive infiltration of surrounding organs, and perhaps metastases. Even when there is considerable infiltration, with incomplete removal, some patients have been apparently cured by postoperative radiation.

Conservative unilateral operations should be limited to unilateral growths in which the capsule of the tumor is intact, and in which there is no evidence of infiltration or metastasis.

In all other cases removal of both ovaries and uterus would seem to the authors to be the preferable procedure.

PERITONEOSCOPY IN DIAGNOSIS

E. B. Benedict³⁶ has made 48 examinations with the Ruddock peritoneo-

scope. There has been 1 fatality, in which pneumoperitoneum may well be considered as a contributory cause of death. The patient was in the terminal stages of multiple lung abscess, coronary disease and possible echinococcal cyst of the liver. An error in judgment was made in subjecting him to the stress and strain of sedative drugs and peritoneoscopy. There have been no other complications except a subcutaneous emphysema in a few cases. No real errors in diagnosis have occurred.

When patients are carefully selected, peritoneoscopy is attended with little risk. Those with serious pulmonary or cardiac disease are not good prospects. Abdominal adhesions may complicate the procedure, but by careful selection of the site of puncture difficulties have thus far been avoided. Peritoneoscopy may be indicated in any abdominal or pelvic condition in which the diagnosis is obscure or in which additional evidence is needed to confirm a diagnosis or to plan treatment. The procedure will frequently give information that will decide for or against laparotomy. Peritoneoscopy is useful in cancer, cirrhosis, tuberculous peritonitis, ascites, pelvic tumors, ectopic pregnancy and ovarian dysfunction.

In 1 case an excellent view was obtained of a polycystic liver, in another case of supposed echinococcal cyst, the liver was found to be normal, and in a third case in which there was a questionable palpable mass, the peritoneal cavity was found to be normal. Serious cardiac or pulmonary disease may be a contraindication, for the peritoneal distention necessary for a satisfactory examination may somewhat embarrass the circulation and the diaphragmatic movements. Because of the danger of spreading infection, peritoneoscopy is contraindicated in inflammatory conditions. Peritoneoscopy will not replace exploratory laparotomy in all

cases, but in certain cases it makes it possible to avoid major surgical operations. Peritoneoscopy requires local anesthesia, a stab incision and hospitalization of 1 day.

STERILITY

Further studies in infertility and sterility and an analysis of 200 couples are reported by I. F. Stein.³⁷ Infertility plays a greater rôle in the present incidence, as 103 matings are so classified as against 97 in the sterility grouping. Primary infertility or sterility occurred about 3 times as frequently as did secondary.

In the list of etiological factors, uterine hypoplasia, tubal obstruction, previous abortion, and chronic endocervicitis continue to play a significant part. The male partner is shown to be directly responsible in slightly over one-third of the cases of sterility, and among the infertilities, substandard sperm specimens were not infrequently revealed. Huehner tests were carried out in 125 couples and, in cases of unsatisfactory results, condom and urological tests were routinely requested. Tubal patency tests were done in 111 cases, hysterosalpinography in 42, and pelvic pneumoperitoneum by the trans-uterine or transabdominal route in 41 cases. Tubal obstruction was encountered in 20, of which 15 were complete and 5 partial. The Rubin test is performed immediately following Huehner's test in suitable subjects as both expedient and practical, and there has been no occasion to regret this practice.

Surgical measures were carried out in 73 patients. Linear cervical cauterization was the most frequently employed measure and has continuously proved to be satisfactory. Occasionally, a second treatment, using the Kimble or Hyam method, was required. Salpingostomy was per-

formed in only 1 case in this series (without benefit) and no tubal implantations were done. The most interesting and most hopeful group from a surgical standpoint is that of 9 cases of sterility due to bilateral polycystic ovaries. In 5 of these, amenorrhea was a feature of the clinical picture. The diagnosis of significant ovarian swellings in each case was established by x-ray after pneumoperitoneum, and bilateral cortical wedge resection resulted in prompt return of the menses, general systemic improvement, and restored fertility.

From the large percentage of pregnancies which occurred in the group here reported, it is apparent that a considerable proportion of the matings were only relatively infertile and the minority were really sterile. There can be but little doubt that, if given time, a certain proportion of apparently infertile women eventually succeed in becoming pregnant without investigation or treatment. In others, pregnancy follows immediately after the Huehner and patency tests are performed and before any other treatment becomes indicated. This fact strengthens Stein's belief that the patency test with gas or with opaque media has therapeutic as well as diagnostic value. Pregnancy occurred in 15.4 per cent of the sterile matings after treatment of one or both mates, and in 49 per cent of the infertile matings. In 5 of the latter, repeated pregnancies occurred. Instruction in sex habits, time of coitus in relation to the estimated fertile phase of the cycle, and general measures have been helpful. Glandular therapy played but a small part, its chief virtue resting in thyroid extract. Estrogenic preparations were used in the treatment of hypoplasia and, despite little change in the uterine size, pregnancy sometimes occurred.

Endocrine Factors—C. Mazer, S. L. Israel, and C. W. Charny³⁸ emphasize

the need for systematic approach to the study of sterility. These investigators report their findings in a thorough study of 389 barren marriages.

Four factors must be investigated and corrected, if need be, in every barren marriage:

1. The male factor, determined by complete study of the semen.

2. The cervical factor: (a) Failure of insemination of the cervix, and (b) hostility of the cervical secretions.

3. The tubal factor, determined by transuterine insufflation or by uterosalpingography

4. The endocrine factor which finds expression in amenorrhea, dysfunctional uterine bleeding, or pseudomenstruation

1 **The Male Factor**—Normal semen, best collected in a glass jar and kept at room temperature, contains a minimum of 60,000,000 spermatozoa per cc with less than 20 per cent of abnormal forms. Ninety per cent of the spermatozoa should remain actively motile for 1 hour and about 10 per cent for 24 hours.

In their study of 389 barren marriages, 158 (40.6 per cent) of the male partners had various types of semen abnormalities. Of this number, 24 (15.2 per cent) had azoospermia, 10 (6.3 per cent) necrospermia, and 124 (78.5 per cent) oligospermia.

Treatment of Oligospermia—Massage of the prostate and seminal vesicles twice weekly over a period of 6 months almost invariably resulted in an appreciable increase of the sperm count probably through reflex stimulation of spermatogenesis, somewhat analogous to the ovulation which follows mechanical stimulation of the cervix in the isolated cat.

Organotherapy in the definitely endocrine group of 22 male patients was disappointing. The gametogenic factor of the anterior pituitary lobe (**prephysin**),

its equivalent obtained from the urine of menopausal women (**gamone**), and the luteinizing factor (**antuitrin-S**) were employed in 21 or 22 patients with improvement of the sperm count in only 2 instances. **Thyroid extract, exercise**, and a **high protein diet** were then tried in 12 of these patients with encouraging results. In fact, 7 of the 12 attained a normal sperm count. Low dosage irradiation of the pituitary gland in 7 of these patients with stigmas of hypopituitarism produced only partial improvement in 1.

2 **The Cervical Factor**—In the complete study of 389 barren unions, repeated examinations following intercourse failed to disclose any spermatozoa in either the vagina or the cervix in 14 cases (3.6 per cent). Failure of insemination of the cervix was most frequently caused by a tight, fibrous, hypersensitive vagina, which is part and parcel of the genital hypoplasia seen in primary ovarian deficiency. Usually enlargement of the vaginal introitus by the Hirst method promptly removes this barrier to reproduction.

In the presence of normal semen the repeated recovery by aspiration of dead or faintly motile spermatozoa from the cervical canal as early as 8 hours after an elective intercourse implies hostility of the cervical secretions. This condition was present in 86 of 389 cases (22.5 per cent). Repeated dilatation of such a pinpoint cervix as an office procedure often abolishes hostility of the cervical secretions and occasionally benefits by reflex ovarian stimulation an associated amenorrhea. Gross cervical infection with viscid mucopus, wherein active spermatozoa become enmeshed and finally lose their motility in the attempt to extricate themselves, is another important cause of hostility of the cervical secretions.

This condition is best treated by means of the cautery.

3. **The Tubal Factor**—Complete or partial occlusion of the fallopian tubes or loss of peristalsis was 1 of the major factors in 213 of 389 sterile marriages (54.7 per cent), exclusive of those women who had palpable adnexal pathology. Of the 213 patients, 149 had partial and 64 complete obstruction of the fallopian tubes. Normal fallopian tubes transmit 90 cc. of carbon dioxide per minute at a pressure of 60 mm. of mercury. When a much higher pressure is required to transport this volume of gas per minute into the peritoneal cavity, the fallopian tubes are damaged. In other words, the accuracy of the Rubin test depends upon volumetric as well as manometric readings. Therefore, the hand bulb method of performing the Rubin test is inaccurate and grossly misleading. Demonstration of tubal peristalsis requires the addition of a kymograph to the standard apparatus. The absence of peristalsis in perfectly patent fallopian tubes is usually the result of an antecedent infection.

The prerequisites for tubal surgery according to the authors are as follows: (a) Elimination or correction of all other etiologic factors, irrespective of their apparent unimportance; (b) failure of numerous insufflations at a high pressure to open the fallopian tubes; and (c) when uterosalpingography shows the occlusion to be bilateral, complete, and at the fimbriated end in at least 1 tube.

Uterosalpingography is indicated when a plastic operation on the fallopian tubes is contemplated. It locates the sites of obstruction and materially facilitates the operation. The therapeutic value of the iodized oil in occlusion of the fallopian tubes is debatable. In this series of cases, uterosalpingography was performed in 13 women with complete tubal occlusion and was followed by pregnancy in 2 instances soon after the procedure.

4 **The Endocrine Factors in Female Sterility**—From the standpoint of study and treatment, endocrine sterility of the female may be divided into 2 groups: (a) Those with amenorrhea or dysfunctional uterine bleeding, and (b) those who menstruate regularly but show a defective premenstrual phase or a total absence thereof.

Treatment of Amenorrhea in Sterility—Successful treatment of amenorrhea depends largely upon the recognition of each of the 3 above-mentioned types. The amenorrhea of purely uterine origin, wherein adequate quantities of estrogen and progestin (the latter in the form of pregnandiol) are present cyclically in the urine, is best treated by injections of estrogen (*theelin, progynon, amniotin*, etc.) in large doses, such as 100,000 I U every other day for 10 days of the month. Intermitent administration of large doses of estrogen corrects the basic endometrial atrophy but does not inhibit the pituitary-ovarian mechanism as continuous treatment does. *Pelvic diathermy* is of value in improving the blood supply of the uterus.

In the pituitary type of amenorrhea (Frohlich's syndrome), a *high protein diet*, not for the sole purpose of reducing weight but mainly because of its stimulative effect on the pituitary gland, is indicated. *Organotherapy*, judiciously employed, is effective in a small percentage of functional pituitary deficiencies. It consists of the administration of both the follicle-stimulating (*prephysin, gamone*) and the luteinizing (*antuitrin-S, follutein*) principles simultaneously every other day for 20 days of the month. The 10-day rest period is employed on the theoretical basis of avoiding the production of antihormones. To obtain results, the dosage must be large. Unfortunately, the commercially available pi-

tuitary and pituitary-like products lack sufficient concentration for effective use.

The administration of small doses of estrogen, such as 2000 I. U. daily by mouth or every third day hypodermically, enough to maintain the blood estrogen at a normal level, aids in overcoming the coexisting hypoplasia of the Mullerian tract and in maintaining the normal peristalsis of the fallopian tubes.

Thyroid extract, even in those with a normal basal metabolism, is a valuable adjuvant because of its stimulative effect on all tissues including the hypophysis and ovaries.

Dilatation of the hypoplastic cervix every other week by passage of graded sounds not only establishes better drainage but also improves pituitary-ovarian function through the nerve pathways.

The primary ovarian type of amenorrhea with a history of antecedent pelvic infection as the probable cause requires pelvic diathermy and ovarian massage, which is possible in the thin individual. Usually, however, amenorrhea caused by primary ovarian disability with a normal or even overactive anterior pituitary lobe is developmental in origin. In such instances, the administration of **insulin** in doses of 10 units twice daily is helpful when employed in conjunction with other measures soon to be described. In this type of amenorrhea, as well as in the pituitary form, small doses of estrogen and repeated dilatation of the cervix contribute toward the ultimate goal.

The most effective single agent in the treatment of amenorrhea as the major factor in a sterile marriage is **irradiation of the pituitary gland and ovaries** in doses of 50 to 80 roentgen units, depending on the weight of the patient. A course of 3 weekly treatments is given to each area and repeated, if necessary, in 2 or 3 months.

Restoration of menstrual periodicity and pregnancy followed low dosage irradiation of the pituitary gland and ovaries in 35 of 38 sterile women with amenorrhea as the major factor in the unproductive unions.

In order to avoid irradiation of an unrecognized early embryo, a pregnancy test, warn the authors, should be done before the treatment is instituted.

The etiology of dysfunctional uterine bleeding in women of childbearing age is identical in most respects with that of amenorrhea and, moreover, yields to almost the same treatment.

Pseudomenstruation is cyclic uterine bleeding, clinically indistinguishable from the normal, from an endometrium totally lacking the secretory (nidation) elements. It is caused by failure of ovulation and subsequent luteinization or by quantitative disproportion in the production of the 2 ovarian hormones, estrogen and progesterin, which successively participate in the preparation of the endometrium for nidation. This condition, rarely present in fertile or potentially fertile women, was found to be the major cause of barrenness in 37 of the 104 women with endocrine sterility.

Theoretically, the administration of the pituitary-like luteinizing principle should correct the condition promptly. Practically, pseudomenstruation is more resistant to treatment than either amenorrhea or dysfunctional uterine bleeding. Only 3 of 8 sterile women with pseudomenstruation conceived after prolonged treatment with the luteinizing principle of pregnancy urine. Thyroid extract was apparently the corrective agent in the pregnancy of 1 and repeated dilatation of the cervix in the other 2. The administration of insulin to the thin individual with pseudomenstruation is advocated by some.

Low-dosage irradiation of the pituitary gland and ovaries, so effective in the

treatment of amenorrhea, proved totally useless in the treatment of 11 sterile women with pseudomenstruation.

In the nonendocrine group of sterile women, repeated transuterine insufflation and office dilatation of the cervix give the best results.

Sterilization of the Female

A method for the sterilization of women by cauterization of the uterine cornu is presented by C. G. Bowers and M. K. Bowers.³⁹ The procedure they claim can be carried out in the office as it is only slightly more disturbing than cervical cauterization. After determining the necessity for sterilization, the patient is requested to be at the office a week or 10 days after her regular menstrual period. She is instructed to take a copious douche of warm soda water an hour before her appointment. Following pelvic palpation she is left in the lithotomy position and a Sims speculum is introduced. The vagina and vaginal wall are thoroughly swabbed with a suitable antiseptic. The plug of mucus occluding the os is removed and the cervical canal is cleaned. A lip of the cervix is grasped with a tenaculum, and a catheter to which is attached a syringe with 10 cc. of radiopaque oil is inserted until its tip passes the internal os and the rubber olive fits snugly into the canal. The oil is injected slowly. The injection is discontinued, but the catheter is retained in position to prevent outflow of oil. A roentgenogram is taken and immediately developed, outlining the cavity of the tubes and uterus.

The electrode employed is about 9 inches (22.5 cm.) long and one-fifth inch (0.5 cm.) in diameter, the distal end is semiflexible and is tipped with a small conical coil of platinum wire. Proximally there are 2 leads for electrical connections. The cauterizing coil at the

tip is of platinum wire. To bring the cautery to a "cherry red" in air it was found that 8, 01 ampere was required, corresponding to a consumption of 0.96 watt. The cautery electrode is then introduced, following the toupe previously outlined by the sound. Its active tip is snugly fitted into the uterine horn and by touch on its shank it is determined to be in contact with the mucosa on all sides. The current is then turned on for about 45 seconds, meanwhile the active tip is given a slow rotary motion of a single revolution. This movement of the cautery tip prevents too deep a burn in 1 spot in the cornu and it causes the cauterization to be distributed about the entire funnel surface of the cornu, causing destruction of all the mucosa in this area and giving assurance against fistulous formation. It is important that the zone of coagulation extend into the muscular wall of the uterus, as it is here that the contracture is produced.

The opposite side is similarly cauterized and a gauze sponge is left in the vagina to absorb the oil and sanguineous exudate, which the patient is instructed to remove when she returns home. Within a few days following the treatment there will be a serosanguineous discharge for a week or so which may necessitate a daily cleansing douche. Six weeks after the cauterization the patency of the tubes is checked either by an insufflation or roentgenologically. If the tube is closed, the cornu will be seen to be dome shaped and no oil will enter the tube. Contraindications for carrying out the procedure include any active infection of the genitourinary system or any chronic infection of the tubes or uterus. Patients with malignant growths, fibroids, polyps and endometritis should not be treated with the cautery electrode. Of a series of 12 patients, 6 were cauterized once, 5 were cauterized twice and 1 was

cauterized 3 times before closure was complete.

UTERUS

Carcinoma

G. G. Ward and N. B. Sackett⁴⁰ report that during the 18 years that they have been treating carcinoma of the cervix with radium at the Woman's Hospital they have salvaged for 5 years 27.4 per cent of the 595 patients seen and 28.5 per cent of the patients treated. In cases of early carcinoma, in which the disease was limited to the cervix, they saved 56.2 per cent, showing the importance of treating the disease in the beginning stages.

For the 359 patients seen over a period of 10 years the absolute cure rate was 17.3 per cent and the relative rate was 18 per cent. In spite of lowered life expectancy, 73 per cent of those who survived 5 years lived 10 years or longer.

The authors believe that the extent of the disease is of greater importance than the type of cell in determining the probability of cure. In their series, early carcinoma had twice the curability of advanced carcinoma, irrespective of the maturity of the cells and of whether they were of the squamous or adenocarcinomatous type.

The high incidence of carcinoma of the stump after supravaginal hysterectomy points to the desirability of doing a panhysterectomy whenever possible if no added risk is involved.

In 108 cases of carcinoma of the fundus an absolute 5-year cure rate of 42.6 per cent was obtained and a relative rate of 45.5 per cent. They believe that a panhysterectomy is the most essential part of the treatment of carcinoma of the corpus and should be employed whenever possible. Combined radiotherapy and hysterectomy seems to us

the most promising method. However, surgical intervention is contraindicated in nearly 50 per cent of the cases, and radiotherapy is our only resource for this group.

There is a great need for comparative studies of the improvement obtained in combining high voltage roentgen therapy with radium therapy, and the conclusions should be based on the absolute survival rate over 5- and 10-year periods and not on generalized clinical impressions. With the adoption of the Coutard fractional technic definite improvement may be hoped for.

Finally, a survey of the 6 statistical reports of their results shows an improvement in the relative 5-year cure rate we have obtained as follows: 1925, 23.6 per cent; 1928, 23.1 per cent; 1930, 25.5 per cent; 1932, 24.8 per cent; 1934, 25.28 per cent, and 1937, 28.5 per cent.

The treatment for cancer of the cervix that Max Cutler employs is essentially similar to that of the Curie Institute of Paris. It consists of 2 integral parts, *intracavitary* and *external irradiation*. For the former he uses an intra-cervical radium applicator containing 50 mg. of radium with a 1 mm. platinum filter. For vaginal irradiation he employs the colpostat, each of the 3 corks containing 10 mg. of radium element filtered through 1 mm. of platinum. From 3500 to 4000 mg.-hours is administered to the cervix and a similar amount to the vagina, so that the total radium dose is from 7000 to 8000 mg.-hours. The cervical irradiation extends over a period of from 70 to 80 hours and the vaginal applicator from 116 to 133 hours.

Curettage

The advantages of diagnostic office curettage is discussed by S. L. Israel and C. Mazer.⁴¹ The operation is per-

formed usually without an anesthetic. The technic employed is as follows:

The vulva and vagina are cleansed with tincture of green soap and water. The portio, exposed by a bivalve speculum, is painted with 3 per cent tincture of iodine and grasped by a bullet forceps. The bivalve speculum is replaced by a weighted one. The cervical canal is then iodized and the direction and depth of the uterine cavity verified by the passage of a uterine sound. In multiparous women, the smallest (No. 1) Sims' sharp curette may then be passed without difficulty. However, in some nulliparous women, the cervical canal is narrow and requires preliminary dilatation. In such instances, the smallest metal dilator, moistened by a sterile water-soluble lubricant, is passed, beyond the internal os. Following this, the curette readily enters the uterine cavity, sedulous care being observed to avoid injury to the neighborhood of the internal os. The interior of the uterus is assiduously investigated and curetted in a routine manner. At the conclusion of the procedure, the patient is permitted to rest on the table for from 10 to 15 minutes and instructed to remain at rest at home until the following morning.

The authors report their experience in 305 patients. Complications occurred only twice, perforation of the uterus in 1 and mild infection in the other. In 258 patients the curettage was employed in the course of functional studies, and in 47 there was organic disease of the uterus, cervix or vagina. Among the latter, there were 5 cases of adenocarcinoma, 4 of these lesions being so early that no cancer was found in the extirpated uteri.

Dysfunctional Uterine Bleeding

It has been widely accepted that functional uterine bleeding is almost invari-

ably associated with endometrial hyperplasia. However, H. W. Jones⁴² calls attention to the fact that in his experience with 83 consecutive cases about 14 per cent were associated with secretory endometrium.

Forty-one cases of functional uterine bleeding associated with secretory endometrium were studied in detail. In most cases the complaint was simple menorrhagia. Secretory endometrium was found during bleeding which lasted for as long as 34 days, and it was also found after prolonged bleeding associated with corpus luteum cysts, suggesting the possibility that with functional uterine bleeding secretory endometrium may persist for a long period of time.

Treatment—Testosterone therapy for dysfunctional uterine bleeding is based on scientific experimental observations. In a report by M. Mazer and C. Mazer (to appear in *ENDOCRINOLOGY*), the effect of prolonged testosterone propionate administered on the immature and adult female rat was studied.

The synthetic androgens, testosterone and testosterone propionate, given over a relatively short period, have been found to stimulate the ovary of the normal rat. Daily hypodermic injections of 15 mg. of testosterone propionate were given for days. In the immature rat single injections of 1 to 5 mg. of testosterone propionate or androstenediol caused follicle stimulation, with or without luteinization, and premature opening of the vagina within 60 to 192 hours after the injection.

Coincident with the ovarian stimulation there was uterine and vaginal growth and suppression of estrus. The vaginal epithelium showed mucification similar to that seen in pregnancy.

Mazer and Mazer investigated the action of the substance in the rat when given over a prolonged period.

In the immature rat prolonged administration of testosterone propionate they found causes a decrease in the weight of the pituitary, adrenals, ovaries and uterine horns and inhibition of estrus with mucification of the vaginal epithelium. The degree of uterine atrophy is not in proportion to the ovarian atrophy, presumably because the suppression of estrogen production is partly counterbalanced by the direct stimulative effect of testosterone on the uterus. The adult rat reacts similarly with the exception that the pituitary gland shows no significant decrease in weight. The deleterious effect of prolonged testosterone treatment on the ovaries is temporary. Restoration of structure and function occurs within 29 days.

Evidence is drawn from the literature and the experiments described that the duration of treatment is the determining factor in the effect of testosterone on the ovaries; short treatment produces stimulation and prolonged treatment depression. It is considered that the ovarian atrophy is secondary to pituitary inhibition.

C. Mazer and M. Mazer report a clinical study of the use of testosterone propionate for this condition. The material comprising this clinical study consists of 25 premenopausal and 13 younger women ranging in age from 22 to 51 years. Twenty-nine of the 38 patients had metrorrhagia for periods averaging 12 weeks with a minimum of 4 weeks. Nine had menorrhagia of varying severity for an average period of 17 months. Thirty of the patients menstruated regularly prior to the inception of the dysfunctional uterine bleeding, 7 had delayed periods, and 1 had a radium-induced menopause 10 months previously.

The therapy consisted of **testosterone propionate** in oil (oreton) administered intramuscularly 3 times weekly

for from 2 to 9 weeks, irrespective of whether or not the bleeding continued. The individual dose was $2\frac{1}{2}$ mg. in 16 patients, 5 mg. in 11, 10 mg. in 7, and 25 mg. in 4 patients. A cure was considered to have been attained if the abnormal bleeding ceased during the period of treatment and did not recur for 4 months after cessation of treatment. The follow-up period varied from 4 to 19 months with an average of 8 months. By these criteria 26 of the 38 (68 per cent) were cured and 12 (32 per cent) were only temporarily or not at all improved by the therapy.

It is evident that testosterone propionate has a definite place in the treatment of dysfunctional uterine bleeding, especially at the menopausal age when the anterior pituitary-like substance is almost totally ineffective, and when larger doses can be employed without risk of permanent damage to the ovaries.

G. L. Foss⁴³ discusses the clinical use of testosterone propionate for the treatment of uterine bleeding. The outcome of animal experiments with testosterone propionate has led to its use as a remedy for excessive and irregular uterine bleeding due to hyperfolliculism in women, especially as Zuckerman's work was fairly conclusive that it caused no undesirable secondary effects, except perhaps enlargement of the clitoris.

Foss used testosterone propionate in 16 cases and found that for most patients total doses of from 300 to 800 mg. are required, according to the severity and duration of bleeding and the nature of the disorder to inhibit endometrial proliferation. In some cases of menorrhagia, cyclic doses of from 20 to 40 mg. given twice a week for a few months are sufficient to counteract follicular overaction or to restore a cyclic rhythm in metrorrhagia. In severe cases

a total dose is required of from 800 to 2000 mg. given in daily injections of 100 mg. or injections given twice a week of from 150 to 200 mg., the individual dosage being adjusted to the clinical history. Metrorrhagia and menorrhagia can as a rule be controlled by injection of testosterone propionate in adequate doses. Two patients have proved refractory to treatment, even with large doses of testosterone propionate. No harmful effect, however, has been noticed in the 16 patients.

Myomectomy

An analysis of the indications and results in 523 cases of uterine myomectomy is presented by V. S. Counsellor and R. E. Bedard ⁴⁴

The study revealed a mortality of 1.14 per cent. During the period 1925 to 1934 about 3400 hysterectomies were performed for myomas, giving a ratio of about 6 hysterectomies to each myomectomy.

There were 294 patients who experienced myomectomy as the primary operation and 229 who were subjected to myomectomy as a secondary procedure.

The operations were performed in each instance as conservative methods to maintain as far as possible the reproductive and menstrual functions. In a few instances, among patients beyond the reproductive period, the adnexa were removed, myomectomy being performed as a secondary procedure; 63.3 per cent of the patients were in the fourth decade of life and the average age of all patients was 36.7 years.

The menstrual periods may be normal among patients who are candidates for myomectomy. In this series the periods were normal in 38 per cent of the cases. Dysmenorrhea was a prominent symptom in 47.4 per cent of the patients who had abnormal menstrual periods.

The situation of the tumor with respect to the uterus is an important factor in performing myomectomy. This is, as far as possible, all myomas should be enucleated through the anterior surface of the uterus or through the anterior leaf of the broad ligament so as to minimize the risk of later intestinal obstruction.

Ovarian disease was associated in approximately the same number of cases as that seen in performing hysterectomy for myomas in general. In this series it was 47.4 per cent.

Myomectomy in pregnancy is indicated only in exceptional instances. There were 22 cases of intrauterine pregnancy in which myomectomy was performed. Of these, 31.8 per cent of the patients had a miscarriage postoperatively. Of those who did not have a miscarriage, 73.2 per cent had normal births; there was only 1 case in which Cesarean section was performed. Myomectomy, therefore, is not to be regarded as too important a factor in subsequent delivery.

The recurrence of myomas in this series was approximately 20 per cent, which is somewhat higher than that currently reported, but is accounted for by the fact that 229 of the myomectomies were secondary procedures. It is of importance that 25 per cent of those less than 40 years of age were known to have recurrences as contrasted with 8.9 per cent more than 40 years of age. Of the group of 111 who had recurrences, only 26 required subsequent surgical treatment.

The incidence of fertility was determined for all patients with the exception of 8, or 2.1 per cent, regarding whom the information was not available prior to operation. This incidence was 61.3 per cent, but 26.9 per cent of the fertile patients had experienced only miscarriages.

Subsequent to myomectomy, 68 of the 409 patients who were less than 40 years of age at the time that myomectomy was performed became pregnant and bore a total of 84 babies. The postoperative fertility was accurately determined for 196 patients less than 40 years of age among whom pregnancy could reasonably be studied, which gives an incidence of 34.7 per cent postoperative fertility. In the presence of a postoperative incidence of fertility of 34.7 per cent, myomectomy in the authors' opinion should certainly be regarded as a favorable procedure during the reproductive period, especially when the mortality is not higher than that associated with radical procedures

Hysterectomy

A study of 1000 consecutive operations performed over a period of 23 years from the public ward of a general hospital by members of the general surgical staff at the Peter Bent Brigham Hospital, Boston, Mass., is reported by S. M. Dupertuis and R. Zollinger⁴⁵. It is their impression that the mortality figures of this study do not justify the routine use of panhysterectomy in all cases, since the incidence of cancer of the cervical stump in this series of 755 supravaginal hysterectomies, as far as could be determined, was only 0.4 per cent. If supravaginal hysterectomy is to be maintained as the operation of choice in the majority of cases, however, more frequent and careful treatment should be given to the lacerated cervix at the time of hysterectomy in order to reduce the danger of cancer of the cervical stump and likewise the incidence of continued postoperative vaginal discharge.

Vaginal Hysterectomy

From an analysis of 348 personal cases without a death, L. Averett⁴⁶ claims that vaginal hysterectomy has the following

advantages over the abdominal hysterectomy:

1. Lower operative mortality and morbidity.

2. Less tendency to peritoneal infection or shock and is therefore suitable in cases that are bad operative risks and in no way a disadvantage to the robust patient.

3. In the treatment of hemorrhagic conditions of the uterus in middle-aged women, the mortality rate in vaginal hysterectomy is as low as that of radium, without the sequelae and relapses; furthermore, possible malignant conditions are, in the former procedure, readily disclosed and eliminated.

4. Convalescence is rapid, the patient is able to eat breakfast and read the daily paper the morning after operation. When hysterectomy alone is done without extensive plastic work, the patient is practically devoid of complaint.

5. The risk of ventral hernia and postoperative adhesions is eliminated.

6. Adequate drainage more easily secured.

7. Less risk of injury to bladder and ureters, providing the bladder is properly freed and elevated at the beginning of the operation.

W. W. Babcock exposes and ligates the uterine and ovarian vessels individually on the sides of the uterus. This enables him to open the anterior and posterior *cul-de-sac* without any special effort, for the peritoneum is incidentally penetrated at the side of the uterus while exposing, ligating, and dividing the vessels. Thus there is little danger of injuring the bladder or rectum and, by proper retraction with a small trowel, the ureters are not endangered. The vaginal vault is also left open and a Mikulicz drain carried into the pelvis. This does away with the secondary pelvic abscesses, but in 3 instances intestinal adhesions to

gauze or some adjacent part led to an obstruction requiring secondary operation. He, therefore, then brought the pedicles through the peritoneum to the vaginal wall where they were anchored, the peritoneum being closed, and the vaginal margins lightly approximated over the pedicles. Thus far, this method has worked well.

J. W. Kennedy states that the indications for the operation are: All fibroid tumors that can be removed by the vaginal route and, if morcellation is resorted to, large growths may be removed through the vagina; all dysfunctions of the uterus in the suspicious and sterile uterus; all degrees of prolapse of the uterus in the sterile organ; all conditions of the abused cervix in patients over 45; in all patients where malignancy comes within the first and second groups; in all polypoid growths of the cervix in patients over 45, as over 60 per cent of these patients will show similar growths of the fundus, and in practically all patients with excessive weight with cardiorenal symptoms. He prefers the clamp method.

The clamp method in removing the uterus is most important in any degree of prolapse of the organ, for after the clamps are removed the broad ligaments contract and pull the vaginal fornix high up and thus relieve the prolapse which takes care of the cystocele in most conditions. In the extensive prolapsed conditions, such as complete procidentia, he immediately does a repair of the cystocele by the use of silkworm-gut sutures.

A slough incident to the clamp method of removing the uterus causes an infectious discharge and buried absorbable sutures must not be used.

The clamp method of removing the uterus lengthens the vagina, the ligature method shortens it. The use of the clamps gives a large percentage of operability. The operative time is the shortest of any

major operation of which he has knowledge. Very often the anesthesia may be stopped when the operator begins the procedure.

VAGINA

Bacteriology—L. Weinstein⁴⁷ examined 419 vaginal secretions for the presence of viable staphylococci. Of 196 pregnant patients and 223 with or without disease of the female genitalia, 191 were found to be harboring staphylococci. Eighty-two of the pregnant and 109 of the nonpregnant women yielded staphylococci. Most of the strains isolated were of the albus type, aureus being found in a much smaller number of cases; 90 per cent as contrasted with 9.9 per cent. No correlation could be established between the incidence of the albus type and any particular clinical syndrome. Staphylococcus aureus was recovered, however, with the greatest frequency from pregnant individuals.

Of the 19 strains isolated, 9 were found in cases of pregnancy, 3 were recovered from cases of *Trichomonas vaginalis* vaginitis, one from an individual with a retroverted uterus, 4 from cases of "non-specific" vaginitis, 1 from an individual with dysmenorrhea and 1 from a patient in whom there was no pathologic change of the genitalia. The albus type of staphylococcus deserves further study in its possible relation to disease of the female genitalia, since many of the types isolated possess the property of hemolyzing blood, occasionally coagulate serum and ferment mannitol which, according to Chapman, are indicative of potential pathogenicity.

Trichomonas Vaginitis

G. P. Hibbert and F. H. Falls⁴⁸ find that a specific strain of streptococcus is an important causative factor in the symptomatology of an infection of the

vagina which has all the clinical manifestations of so-called *Trichomonas vaginalis* vaginitis but which fails repeatedly to reveal the presence of the parasite in the discharge, postmenstrual or at other times.

The organism isolated from their cases has been positively identified as the *Streptococcus subacidus* of Holman. *Streptococcus subacidus* as a pathogen was proved in their work by experimental inoculation of 4 out of 5 patients with a pure culture of the organism. Objectively the symptoms produced were intense redness of the cervix, vaginal mucosa and vulva, and a gray-white, sticky discharge. Subjectively the patients all complained of a tenderness, burning and itching about the vaginal orifice, and a whitish discharge.

Treatment—The treatment instituted was as follows. At no time was any bacteriocidal agent applied to the vagina, the vaginal tract was first cleansed of accumulated debris with dry, sterile cotton. Then a sterile cotton tampon saturated with a *broth filtrate of the Streptococcus subacidus* was packed against the cervix and allowed to remain in place for 24 hours before removal by the patient. An intradermal injection of a *standardized vaccine* made from the *Streptococcus subacidus* was also given at this time. The interval between treatment was 1 week, and the treatments were discontinued during menstruation. All 4 of these patients were successfully treated and rendered symptom-free in from 4 to 7 treatments.

The authors believe that the *Streptococcus subacidus* found in patients presenting the clinical picture of *Trichomonas vaginalis* is pathogenic, as shown by its fulfillment of Koch's laws. It produces an immune reaction (agglutination) when injected intradermally.

Local clinical improvement was more rapid and apparently more lasting when general antibody reaction was stimulated by the vaccine in addition to the local antibody stimulation by the filtrate.

The pH of the vagina was found to be relatively high when there were large numbers of *Streptococci subacidus* present, and to be lower as they disappeared, irrespective of the presence or absence of the trichomonads.

The disappearance of the clinical picture and symptoms with the disappearance of the *Streptococcus subacidus*, occurring in the presence of the trichomonads, suggests the former as the chief factor in the production of the lesions.

Further efforts to eradicate this streptococcus from the genital tract, and to raise the general immunity to this organism, seem the logical way to the authors to attempt the control of this infestation.

E. L. Cornell⁴⁹ recommends the following treatment. The patient is given 100 tablets of a preparation containing *acetarsone (Devegan)* and instructed to insert 1 tablet in the vagina nightly after retiring. The patient is warned against having sexual intercourse throughout the course of treatment unless a condom is used. She is not to take douches. She should keep the labia clean by frequent washing since the tablet disintegrates and is discharged from the vagina. If allowed to dry on the hair, it is difficult to remove. The patient is to return to the office on the first, third and fifth day of her menstrual period. At this time the menstrual secretions are cleansed out and 3 or 4 tablets are inserted into the upper part of the vaginal vault. When the period is finished, the patient may resume home treatment.

After the fourth menstrual period, the home treatment is discontinued, but the patient is to return to the office 1 week after she stops flowing. The secretions

at this time are cleaned out and, if *Trichomonas vaginalis* is not found, the patient is instructed to return in 10 days for a retest. If the test is negative again, the patient returns again after her next menstrual period for another test. The patient is considered cured if no evidence of *Trichomonas vaginalis* is found on this visit.

If a patient who has finished the course of treatment and has been pronounced cured suffers a recurrence of vaginitis following sexual intercourse without the use of the condom, the husband should be considered a trichomonas carrier even though the organism is not found in his prostatic secretions. He should be given treatment. The woman should be treated in the same manner as before for at least 2 or 3 months and retested thereafter.

VENEREAL LYMPHOGRANULOMA

A study of 46 negroes with venereal lymphogranuloma is presented by L. W. Shaffer and E. Arnold.⁵⁰ The commonly accepted methods of treating the disease were entirely unsatisfactory. With the introduction of sulfanilamide and its use in greatly diversified infections, it was used in this infection in 22 cases. The drug was given entirely by mouth, 40 grams (2.6 Gm.) daily in 4 doses of 10 grams (0.65 Gm.) each for 1 week, 30 grams (2 Gm.) daily in 3 doses of 10 grams each for the second week, and 20 grams (1.3 Gm.) daily in 4 doses of 5 grams (0.3 Gm.) each for the remainder of the time. The usual length of treatment was from 1 to 2 months. The results with such small doses have been encouraging. Of the 12 cases in which sulfanilamide alone was used, apparent cure occurred in 3, improvement in 5 and no improvement in 2; the results in 2 are unknown. Of the 10 cases in which

there had been previous treatment (usually intradermal injections of Frei antigen, administration of antimony and potassium tartrate, treatment for co-existing syphilis or a combination of these, none of which produced material benefit), seeming cure occurred in 1, improvement in 6 and no improvement in 1; the results are unknown in 2.

The rapid symptomatic improvement in the majority of cases, even of severe chronic involvement, is gratifying. Longer observation will be necessary to determine the permanence of these results. The seemingly specific results may be due to action of the drug on the secondary invaders rather than on the specific virus of the disease. Sulfanilamide may be an effective weapon also in the prophylaxis of venereal lymphogranuloma.

Some practical questions on this venereal disease are answered by W. Frei.⁵¹

What formerly were considered as 4 separate diseases are now combined into the picture of venereal lymphogranuloma, namely (a) The so-called strumous or scrofulous bubo, known especially to the European venereologists and related particularly to tuberculosis or chancreoid, (b) the so-called climatic bubo, known to tropical and naval physicians and associated by most of them to the climate of the tropical countries, (c) the so-called esthiomene, a kind of chronic ulcer and elephantiasis of the vulva related by most of the earlier venereologists and gynecologists to cancer, tuberculosis of syphilis, and (d) the so-called inflammatory rectal stricture related by surgeons to gonorrhea, syphilis or other diseases.

Venereal lymphogranuloma is found in all countries and in all races, although it is rarer than syphilis and gonorrhea.

A question of special importance is the distribution of venereal lymphogranuloma in the sexes. The bubo form of the disease occurs much more often in males,

the elephantiasic and ulcerative form more often on the genitalia and rectum of females. It has seriously been discussed whether these elephantiasic and ulcerated forms represent an infectious stage of the disease. Most authors believe it does, but Frei is still not totally convinced. This question is of great epidemiologic importance, because quite a few prostitutes are affected with these incurable manifestations for many years without discontinuing sexual intercourse.

Of greatest importance in the spread of venereal lymphogranuloma is the so-called primary lesion on the genitalia, the beginning of the disease. Later on when the bubo has fully developed there is ordinarily less danger of transmission by men. Abortive and inapparent forms, which are known to exist, offer a dangerous source of infection even for years. There are several little endemics known to have been started by a single woman who had only slightly enlarged inguinal glands and a mild discharge and gave a positive cutaneous test.

Venereal lymphogranuloma begins with an average incubation of from 10 to 25 days but occasionally after a period of some months. In a large number of cases the first sign is a small lesion at the portal of entry, generally the genitalia, the so-called lymphogranulomatous chancre, usually not noticed by the patient. The iliac glands often participate in the disease. In females the bubo process can develop unnoticed inside the pelvic girdle. During the extirpation of buboes in venereal lymphogranuloma, one sees that the central lymphatic vessels take part in the disease.

For diagnosis of venereal lymphogranuloma the most frequently used method is the cutaneous test of Frei. The material needed consists of the diluted and sterilized pus of proved, nonruptured pure buboes of venereal lymphogranu-

loma. One-tenth cubic centimeter is injected intracutaneously and the reaction is read after 2 days. In a positive case, one finds an inflammatory papule of at least 0.5 cm in diameter, often with peripheral erythema and sometimes with central pustule. In negative cases there is no or very little reaction after 2 days. Only tested vaccines corresponding to these conditions should be available for general use. On account of the possibility of generalized or focal reactions, it is not advisable to make the test in peracute stages of the disease or in cases in which suppuration occurs near the peritoneum.

A positive reaction does not prove that the disease still exists, because the power to react to the test remains in healed cases for decades. A negative reaction in cases of venereal lymphogranuloma occurs in the earliest stage of the bubo and in some cases in which there is transitory or constant anergy. In cases of anergy, a positive result may be obtained by the so-called inverted test, in which the patient's sterilized pus is injected into the skin of a patient with proved venereal lymphogranuloma, producing a positive reaction, or the usual vaccine is injected intravenously instead of intracutaneously into the suspect and if he has the disease he may respond by a generalized febrile reaction. It may be said that the venereal lymphogranuloma cutaneous test results in about 95 per cent of positive reactions when buboes have developed and in about 90 per cent when there is ulcerative elephantiasis.

Since the vaccine is of human origin, it is often not available in sufficient quantities, because in many of the cases there is little and sometimes no pus. Therefore some investigators have introduced vaccines of animal origin. Levaditi of the Institut Pasteur in Paris and Jonesco-Mihaiesti of Bucharest produce a vaccine from monkey brain. Grace and Suskind,

of New York, and D'Aunoy and von Haam, of New Orleans, recommend vaccines made from mouse brain.

Treatment—There has been until now no really effective chemotherapeutic method for the treatment of venereal lymphogranuloma. Frei uses *antimony* or *gold compounds*; others use also *copper*, *iodine*, or *salicylic acid* preparations. Only in the earliest stages or in very mild forms of bubo can one obtain abortive healing with these treatments. But one has to keep in mind the fact that some of these bubo forms have a tendency to heal without any treatment. If the bubo has grown larger, an acceleration of healing is sometimes obtained by these medications. But in severe forms of bubo as well as in elephantiasis, no definite effect is obtained by chemical treatments. The antisyphilitic remedies such as arsphenamine and compounds of bismuth or mercury usually do not give any relief in venereal lymphogranuloma. Only in a few of the cases connected with syphilis does one see improvement.

The therapeutic use of *venereal lymphogranuloma vaccine* had according to Frei but little effect as long as the vaccine was injected intracutaneously or subcutaneously. Since the introduction of the intravenous method by Hellerstrom, accelerated healing has been seen in the cases in which there are buboes and sometimes a decrease of complaints in the ulcerative forms.

Some authors recommend the surgical method as the best treatment for the different forms of venereal lymphogranuloma. They extirpate the affected lymph glands in the early and even in the later stages; they extirpate excessive forms of elephantiasis labia majora while treating the chronic ulcerations with intensive coagulation diathermy. On the surgical treatment of rectal stricture there are 2 different opinions. Most physicians re-

strict themselves to inducing a preternatural anus as high as possible; only few prefer radical operations. In some rectal cases fairly good results can be obtained with careful, conservative treatment by very cautious dilations and mild irrigations and regulation of diet and bowel movements.

Roentgen treatment gives, perhaps, some results in bubonic cases, especially when combined with other treatment. In cases in the chronic ulcerative stages there is very little effect and in elephantiasis none. Experience with radium treatment is too limited for any conclusions to be drawn. Ultraviolet rays applied generally and locally may be tried occasionally in ulcerative elephantiasis cases.

A comparison with syphilis, the only venereal disease in which prophylactic measures have had really great success, shows that weapons against venereal lymphogranuloma must be improved in 2 directions. In the first place, in syphilis there are 2 diagnostic methods, the serologic reactions in advanced stages and the dark-field examination for spirochetes in the early and infectious stages. In venereal lymphogranuloma an equivalent convenient method for the examination of the early stages and infectiousness is lacking and has to be worked out with the help of present and future experimental observations. Secondly, in syphilis there are drugs which enable one to destroy the infectiousness in the shortest possible time. In venereal lymphogranuloma such treatment is lacking and has to be searched for by interrelating chemical and animal studies.

VULVA

Chancroid

Chancroidal infection in the female is discussed by R. Torpin and R. B. Dienst.⁵² In the treatment of this lesion,

H. ducreyi vaccine administered subcutaneously is held to be useful in developing immunity and terminating the lesion. Frequently repeated intradermal tests, using 0.1 cc. of vaccine, are of great value in treatment. In addition, it is of the utmost importance to keep the ulcers free from secondary infection by sodium perborate, peroxide, or other cleansing washes. The use of local applications of a mixture of 4.5 per cent *neoarsphenamine* in equal parts of glycerine and cod-liver oil is almost specific for eradicating fusospirochetes in the chronic deeply excavating cases; antigenic therapy is of little value until this is done. Buboës should not be incised, surgical treatment should be limited to *repeated aspiration* when the buboës soften. Not infrequently the pus is sterile and, if buboës are incised, secondary infection is almost certain to follow, often resulting in deep chronic penetrating and spreading ulcerations.

Pruritus

The treatment of pruritus ani by *alcohol injection* was developed by Harvey Stone and first reported in 1916. In 1926, after 10 years' experience with the method in over 200 cases of pruritus ani, Stone concluded that the subcutaneous injection of 95 per cent alcohol properly performed by the technic he described would give prompt and complete relief in all cases of pruritus ani. The results as a rule are not permanent.

After successfully employing Stone's procedure of therapy for pruritus ani for several years, W. M. Wilson⁵³ decided to try the same method of treatment for pruritus vulvae.

Technic—The patient is placed in the lithotomy position, and the vulval and perianal regions are prepared as they would be for surgical treatment except that shaving is not necessary. If one has not previously mapped out the area of

pruritus, the vulval structures and the contiguous surfaces of the skin should be reviewed to determine the exact extent of the itching. The patient will often point to the areas of most intense itching and neglect to mention parts less involved. She should, therefore, be carefully questioned.

The patient is then anesthetized, general anesthesia of some sort being preferable. In the majority of cases in this series the injection was done during nitrous oxide or ethylene anesthesia. During the past year, however, Wilson has employed evipal anesthesia in selected cases and finds it adequate for this brief procedure, which usually requires from 5 to 10 minutes for completion. Local anesthesia may be employed, but except for the injection of small areas, infiltration anesthesia is a tedious, time-consuming procedure which is not well tolerated by women of the type affected. Moreover, the ultimate results are seldom as good as when general anesthesia is employed. If one employs local anesthesia, a minimum amount of solution should be used and alcohol injection delayed until the anesthetic solution appears well absorbed. The purpose of these precautions is to prevent a dilution of the 95 per cent alcohol, which, if great enough, interferes with its destructive action on the subcutaneous nerves.

Wilson has substituted absolute for 95 per cent alcohol in a few cases but could detect no difference in the immediate or the ultimate results obtained. The alcohol is injected by means of an ordinary 2 cc. hypodermic syringe which is calibrated in minims. Any hypodermic needle of small gauge is satisfactory. The author generally uses a No. 25 gauge, $\frac{1}{2}$ inch needle. The needle is inserted perpendicular to and through the skin, so that the alcohol will be deposited just beneath the dermis in the subcutaneous connec-

tive tissue. An injection into the skin itself or too deeply into the subcutaneous tissues may produce a slough. Only from 2 to 4 minims (0.12 to 0.24 cc.) of alcohol is injected at a single insertion of the needle. The number and the spacing of injections depend on the extent of the pruritus, the age of the patient and the condition of her peripheral circulation as well as the estimated efficiency of the circulation of the part to be injected. Elderly patients with arteriosclerosis or vulval and anal varicosities should be given injections cautiously, with a minimum of alcohol (not over 2 minims), at slightly wider intervals than younger women with efficient vascular systems. When the circulation seems unimpaired one may inject as much as 4 minims of alcohol beneath every square centimeter of the pruritic skin.

Immediately after injection the labial folds, particularly the labia majora, become more or less edematous. The edema may reach its height in a few hours or may increase slowly, reaching a maximum in from 12 to 24 hours. After 24 hours it subsides slowly, so that in from 3 to 10 days the vulva usually appears normal, though there is always a certain amount of subcutaneous induration in the region of the labia majora. This likewise subsides slowly, leaving in some cases a chain of small hard nodules, which in turn become smaller gradually and disappear in from 4 to 6 weeks.

The itching usually stops immediately, though occasionally 1 or 2 small areas of pruritus remain. These are usually areas that were overlooked or improperly treated, and they can be reinjected with the patient under local anesthesia if the itching persists after the edema subsides. As a rule this residual pruritus subsides in a few days or can be controlled with antipruritic ointments until it ceases to annoy.

The patients are instructed to remain in bed for at least 2 or 3 hours after injection and to go to bed as soon as they reach home. If the vulval swelling becomes uncomfortable, hot magnesium sulfate packs may be applied. A number of women have resumed their usual occupations on the day following injection, while some with marked edema of the vulva have found it necessary to remain at rest for 2 or 3 days.

Results — Twenty-five patients (51 per cent) had complete relief. Four patients experienced partial relief. There have been 13 recurrences (26.5 per cent) in this series. Alcohol injection failed to relieve pruritus in 2 cases (4 per cent).

The author claims that alcohol first induces degenerative changes in the subcutaneous nerve fibers resulting in a cutaneous anesthesia which persists until regeneration occurs. Second and probably more important, the changes actuated in the vascular and the reticulo-endothelial system result in a rapid mobilization of polymorphonuclear leukocytes and histiocytes, which repair inflammatory processes and thus dispose of the factors principally responsible for the pruritus as well as the cutaneous lesions usually present.

Resection of Sensory Nerves — B. Usher and A. D. Campbell¹⁷⁴ discuss resection of the sensory nerves of the perineum which they performed on 8 patients in whom pruritus proved refractory to nonsurgical measures. The technique described by Learmonth, Montgomery and Counsellor was adopted. While it is true that regressional changes do occasionally follow resection of the perineal sensory nerve, one must not lose sight of the fact that carcinoma in this region commonly follows leukoplakia, with pruritus the only symptom and excoriation from trauma the only visible lesion. On the other hand, if biopsies taken at the

time of the nerve resection do not reveal malignant changes this procedure will relieve symptoms and does not preclude vulvectomy for carcinoma of the vulva if and when detected.

Complete relief has been obtained in 5 of the 8 patients for periods varying from 5 months to 2½ years. In another case there was complete relief for 2½ years, when vaginitis and leukorrheal discharge resulted in a slight recurrence which rapidly subsided under appropriate treatment. The patch of leukoplakia had also disappeared. In 1 patient the nerves could not be excised completely. Relief from symptoms was obtained in the remaining case, but the period of post-operative observation is as yet too short to permit the outcome to be determined.

The patients have not been followed sufficiently long to determine whether the relief will be permanent. In the majority of cases in which operation was performed, local applications, roentgen therapy and endocrine therapy had been employed previously without success.

Vulvovaginitis

Treatment — *Estrogenic Hormone*

—The present routine of treatment of gonococci vulvovaginitis in children is described by R. W. Te Linde⁵⁵

The mother is told to wash the vulva at the daily bath, but no vaginal irrigations or instillations are used. She is then given a demonstration of how to introduce a suppository into the child's vagina. The suppositories of *amniotin* for children which are now on the market contain 1000 I U and have proved most satisfactory. In almost every instance they can be inserted into the child's vagina without difficulty. One suppository is introduced daily at bedtime.

The patients are brought back to the clinic at weekly intervals, when vaginal smears and washings are made. The

washings are made with a small medicine dropper and examined under low magnification. As soon as the vagina is well under the influence of the estrogen, epithelial desquamation begins. At times this is so profuse as to cause the mother to fear that there is an increased amount of pus. But as soon as this epithelial response takes place, the vulval reddening begins to clear up, and in a few days the smear usually becomes negative. Smears are stained by the Gram method, so that the gonococci can be differentiated from gram-positive cocci of like structure.

After the negative smear, the treatment is continued for 2 more weeks, and if the weekly smears continue to be negative it is discontinued. In the average case, the entire treatment extends over about a month. It is possible that in some cases treatment could be discontinued in less than 2 weeks after the smears become permanently negative, but since the author has been following this routine, recurrences have been rare, whereas when he discontinued treatment sooner, in his earlier studies, they were more frequent. The clinical use of this substance in the treatment of vaginitis is harmless.

In his cases of hypodermic administration, Te Linde observed definite hypertrophy of the breasts in most of the children who received any great quantity of amniotin. On the other hand, the children who received amniotin vaginally showed no changes in the breasts. This difference suggested that when the substance was administered by the vagina there was little general absorption and that the more marked effect noted in the vaginal mucosa might be due to greater local concentration. In rare instances there is some general absorption.

The last word concerning the possible harmful effect of estrogenic substance cannot be said until a group of children

treated with it have reached maturity and borne children. At this time, however, it is possible to say that all of the children so treated seem to be developing normally as far as can be determined by examination of the external and the internal genitalia.

Of the 175 children treated, 2 have reached or passed the age of 13. One of these began to menstruate 10 months ago and has menstruated regularly since. The other, at 14, has just had her first period. Another child had her first period 3 months ago, at 11 years, and has menstruated regularly since.

The author also observed that although the vagina could be changed from its normal average acidity of pH 7.5 by means of vaginal suppositories of *florquin* as advocated by Karnaky to a pH 5.7; *i e*, beyond the acidity at which the gonococcus will grow *in vitro*, the results in clearing up the infection were much less satisfactory than with amniotin.

The simple healing of the ulceration and the complete covering of the vagina with a thick adult type of epithelium following the use of amniotin suppositories has an important part in the eradication of the infection.

A follow-up of his first 100 patients, from 3 months to 2½ years after the last treatment, showed 98 of them well.

Sulfanilamide — Before the use of sulfanilamide, the treatment of gonorrheal vulvovaginitis consisted mainly of chemicals applied locally and the use of biologic agents. Since 1928, S. J. Hoffman, M. Schneider, M. L. Blatt, and R. D. Herrold⁵⁶ have used various chemicals locally, such as *silver nitrate*, *mercurochrome*, *acriflavine*, *potassium permanganate*, *merthiolate*, *metaphen*, *ammoniated mercury* and *lactic acid*. Of all these local applications they obtained the least discouraging results with the silver nitrate in 0.5 to 1 per

cent strength in 10 per cent gelatin. With this treatment they obtained negative smears in some instances in from 6 to 8 weeks, which result was considered very satisfactory at that time. Most infections remained positive for more than 5 months. In a series of 124 patients that they treated at the Cook County Hospital the average length of stay in the institution was 4.6 months. Recurrences were very common. Forty of the patients returned because of recurrent infection in from 2 weeks to 8 months after discharge from the hospital. Undoubtedly many more had relapses but did not return.

A temporary wave of enthusiasm followed the introduction of biologic products in the treatment of gonorrheal vulvovaginitis. In 1930 they reported a large series of cases treated with immune horse serum, gonotoxin broth filtrates injected intracutaneously and subcutaneously, ectoantigen intracutaneously, whole gonococci intracutaneously, and local application with gonotoxin. In 1934 they reported on lysed gonococci in the treatment of gonorrheal cervicovaginitis. In general the results were not particularly encouraging with any of these methods of treatment.

The authors treated 18 patients with theelin, giving 2000 I. U. 3 times weekly. The amounts used in individual patients varied from 64,000 to 184,000 units. In general the results were somewhat better than with the silver nitrate treatment, but still not very encouraging, since 40 per cent of the patients had recurrences.

One of the authors, Herrold, has found that *sulfanilamide* in concentrations stronger than 1:10,000 is bactericidal *in vitro*, although such determination must be made in periods of hours to demonstrate gonococcal action instead of the standard 20-minute contact as used with other antiseptics.

The series reported includes a group of 25 children varying in age from 3 months to 10 years. Three of this group had chronic infections at the time of institution of treatment, 1 subacute and the remainder acute infections. No local treatment was used and sulfanilamide was administered orally in fruit juice to all the patients.

During the first 2 days, the daily dosage was $\frac{3}{4}$ grain (0.05 Gm.) per pound of body weight in 4 equally divided doses at intervals of 6 hours. During the next 5 days the dosage was reduced to three-fourths of this amount, or $\frac{9}{16}$ grain (0.04 Gm.) per pound daily. During the second and third weeks the dosage was reduced to $\frac{3}{8}$ grain (0.024 Gm.) per pound daily or one-half the initial dosage. At the end of a 3 weeks' course of treatment a rest period of 1 week was given regardless of the results of smear examinations. All patients whose smears were positive at the end of this rest period were given a second course exactly like the first. A rest period was also given at the end of the second course of treatment, and for the majority of patients who were still infected at the end of the second rest period a third course of treatment was prescribed. A few patients were given a fourth course of treatment after the third rest period.

The authors report that only 7 patients were apparently cured during the first course of treatment, or under a period of 21 days. By apparent cure they mean a clinical disappearance of all signs of infection from the urethra, vagina, cervix and rectum, as well as negative smears from these areas. None of this group of 7 were cured under a period of 16 days, and the average was 17.3 days. Four of the group cured during the first course of treatment had acute infections, 2 chronic and 1 subacute. During the second course of treatment, 9 additional pa-

tients were cured between the thirty-fifth and forty-ninth day of treatment, with an average of 42.9 days. Seven of the 9 patients not cured were given a third course of treatment and 1 of this group was cured during the third course, or in 63 days. Four of the 6 remaining patients not yet cured were given another course of treatment after the usual rest period, and only 1 of this group of 4 was cured by such additional treatment. Analysis, therefore, reveals that approximately two-thirds of the patients were cured by 1 or 2 courses of treatment, after which there was a very marked drop in the percentage of benefit derived by a third and fourth course of treatment. It would seem then that patients who do not respond to 2 standard courses of treatment have gonococcic infections that are relatively resistant to therapy with sulfanilamide.

All patients in this group were kept in the hospital for 2 weeks after negative smears were obtained, and all those listed as cured had follow-up examinations from 1 to 3 months after discharge from the hospital. The examinations revealed that they were symptomatically normal, and smears were negative for gonococci.

The incidence of side reactions was strikingly less than in any comparable series of adults that have been reported. Gastrointestinal symptoms which so commonly occur in adult patients were entirely absent in this group of children. Only 1 patient had a typical "drug fever" reaction, which occurred on the tenth day and was associated with urticaria and swelling of the face. Two other patients had a slight fever of less than 100° F. (37.8° C.). One patient had a rather severe epistaxis, and 3 others mild epistaxis. A definite anemia occurred in only 1 patient.

Summarized, therefore, in a series of 25 patients who were given sulfanilamide,

7 were cured in an average of 17.3 days and 9 in an average of 42.9 days. Only 2 of the 9 remaining patients were cured by additional administration of sulfanilamide.

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OBSTETRICS

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ABORTION

Habitual Abortion

Treatment—M. F. Potter¹ performed a series of Aschheim-Zondek tests on the urine of 19 pregnant women who had previously been unable to carry a pregnancy to term, to see whether the reactions differed from the reactions obtained from the urine of normal pregnant patients. Although the urine of pregnant women who produced stillbirths and abortions frequently gave perfectly normal Aschheim-Zondek reactions, the results were definitely weaker than those with the urines of normal pregnant patients. The 19 patients with a history of habitual stillbirth and abortion were placed on large oral doses (up to 18 grains, or 1.2 Gm., daily) of corpus luteum (*progestin*). Three of these cases ended in failure. There were 6 cases of threatened abortion in this series, in each of which the pregnancy was preserved.

This series of cases of habitual stillbirths and abortions gives a high percentage of pregnancies successfully terminated, especially compared with what the same patients accomplished unaided by *progestin*. Without this treatment the 19 patients had among them 55 pregnancies. Of these only 8 were successful and 47 ended in failure. The same 19 patients, under treatment with *progestin*, achieved success with 16 pregnancies and only 3 failed. It is suggested that the factor in the corpus luteum responsible for these successes is probably different from the factor responsible for the structural changes of the endometrium preparatory to pregnancy.

The treatment of 8 cases of habitual abortion by *progesterone* is discussed

by C. A. Elden.² The general method of treatment followed was the intramuscular injection of progesterone, weekly, as soon as pregnancy was established up to, and including, the sixth lunar month of gestation.

The causes of habitual abortion are many and varied, and the lack of the hormone produced by the corpus luteum is only 1. Hypovitaminosis, hypothyroidism, defective decidual reaction, malformation of the ovum are a few of the causes other than chronic systemic disease.

The matter of dosage necessary to maintain pregnancy in the human being is at present empirical. The series reported by the author shows that from 10 to 44 units were successfully employed through 6 lunar months. No other form of endocrine therapy was used. There was 1 failure due to an operative laceration of the cervix, and 1 not as yet accounted for. Half of the patients had spotting, and 1 had spotting with cramps. All infants were apparently normal with the possible exception of Case 3. Smaller amounts of the hormone than 1 unit weekly may be sufficient to carry a pregnancy to term.

Threatened Abortion

Treatment—E. Shute³ discusses the most suitable dosage of ether extracted or cold-pressed *wheat germ oil*. He has found this to be 12 drams (48 cc) inside of the first 24 hours of treatment, followed by at least 1 dram (4 cc) each day. The dosage varied with individual requirement, the quality of the oil used, and the stage of pregnancy.

A state of hypovitaminosis E appears to be relatively common among the pregnant women of this country.

Enormous doses of wheat germ oil seem to produce no untoward symptoms.

Of 39 women requiring huge doses of wheat germ oil, 28 were hypothyroid cases.

Six instances of idiosyncrasy to wheat germ oil are recorded.

The author further notes in view of the recent report by L. G. Rowntree, A. Steinberg, G. M. Dorrance and E. F. Ciccone⁴ on the sarcogenic properties of crude ether-extracted wheat germ oil in rats, that the study of patients treated with wheat germ oil was begun nearly 4 years ago. For the first 2½ years, an ether-extracted oil was used, since that only a cold-pressed oil. Of the 127 patients, 1 has developed malignancy. She revealed chorionepitheliomatous change in what was grossly a hydatid mole found 10 months after the termination of a pregnancy in which she has been given an ether-extracted wheat germ oil in small doses for the final 6 weeks.

Shute points out that Rowntree's report suggests a certain species specificity in the rat for his oil-produced tumor. He and his colleagues did not find such tumors produced with cold-pressed wheat germ oil. Moreover, they found the tumors developed in the susceptible species only upon administration of oil containing sediment and when the oil was given in doses enormously greater in proportion to weight than have ever been fed to human beings. As rancidity, which rapidly destroys vitamin E, did not affect the sarcogenic power of their oil, it appears that the vitamin itself cannot be blamed for the production of the neoplasms.

In further studies, E. Shute⁵ discusses more of the therapeutic possibilities of wheat germ oil. He would even venture to state that every pregnant woman should take wheat germ oil to prevent abortion. In the past 4 years he has

treated 12 miscarriages and 17 abortions with wheat germ oil. Miscarriage was prevented in 91 per cent and abortion in 88 per cent of the group of patients so treated.

If it is true, argues Shute, that vitamin E acts largely through its antagonism to estrogenic substances in the blood, then it should have a place in the therapeutic fields now occupied by pregnancy urine gonadotropic hormone, thyroid extract and progesterone. He has used it successfully in a very small number of cases of dysmenorrhea which were associated with a high blood content of estrogenic substance, based on the analogy between its action and that of progesterone. Vaginal and anal pruritus have been helped by it in women whose blood showed estrogen excess.

Failure with this mode of therapy may be ascribed to inadequate dosage, personal idiosyncrasies leading to inadequate assimilation, associated hypothyroidism, failure to allow for seasonal depletion of the body depots of vitamin E, rancid oil which has been kept at too high a temperature or allowed to deteriorate with age. Furthermore, many abortions may not be due to vitamin E deficiency or excess of estrogenic antiproteolytic substance in the blood at all, but to other factors such as infection, trauma, sperm abnormality, etc.

Shute does not believe that lettuce, spinach, watercress, and other such green foods rich in vitamin E can be used as a substitute for the latter when plentiful.

As so many aborted fetuses are deformed, the question arises as to the advisability of wheat germ oil therapy designed to prevent abortion. The author indicates that such therapy is probably justified.

In a further study of wheat germ oil therapy E. Shute⁶ warns that the drug

should be kept cold to prevent deterioration. Even when so kept, in bulk or in capsules, it retains its potency very little longer than 8 weeks. The author believes that a more sensitive test of E potency than the classical rat assay is the clinical response of a very common type of pregnant human patient, 1 having an incipient toxemia of the kind which frequently terminates in premature placental detachment. Most of these women have enough E to carry the fetus to term, but they do not have enough to prevent the appearance of toxemia of this particular sort. Wheat germ oil suitable for use in human pregnancy should do more than preserve pregnancy in the rat or in the human being; it should protect the latter from this toxemia.

As to its influence on labor, the administration of wheat germ oil up to term does not delay the onset of labor nor prolong the duration of labor.

Green foods, such as lettuce and watercress, do not replace wheat germ oil in the treatment of the pregnancy complications related to deficiency of vitamin E in the human being. Milk may be an important factor in the diet as concerns its content of vitamin E.

The author observed that human males as well as females show a seasonal variation in the estrogenic substance in their blood, and hence in their assimilated vitamin E. This may have some bearing on male sterility.

Induction of Abortion by Estrogen

A. S. Parkes, E. C. Dodds and R. I. Noble⁷ studied the effect of 2 estrogenic substances (from 0.25 to 1 mg. of ethinyl estradiol and from 1 to 4 mg. of diethylstilbrestrol) given orally to suppress the action of progesterone and to prevent pregnancy. The substances were fed to rabbits in propylene glycol solution,

which was swallowed readily. They found that small doses of orally active estrogen will prevent implantation of the blastocyst if given soon (2 to 7 days) after ovulation or may terminate established pregnancy. The effect is produced in what is essentially a physiologic manner; the luteal phase of the cycle is suppressed and another phase is induced which, though not abnormal in itself, is unsuitable for the development of the embryo. Everything that is known about the menstrual cycle of primates suggests that its hormone control is the same as in lower animals and it is extremely probable that the factors governing the implantation of the fertilized egg are fundamentally similar in women. The conclusions arrived at should thus be applicable to women, though the fact that very large amounts of estrogen are excreted by pregnant women makes it likely that the period during which estrogenic treatment might be effective would be relatively much shorter than in rabbits.

ANALGESIA IN OBSTETRICS

W. A. Ruch⁸ reports on further studies with dilaudid-scopolamine during the first stage of labor. The method employed is as follows. $\frac{1}{32}$ grain (2 mg.) of dilaudid and $\frac{1}{130}$ grain (0.5 mg.) of scopolamine are administered subcutaneously when the cervix is dilated $3\frac{1}{2}$ to 4 cm. in primiparae and $2\frac{1}{2}$ cm. in multiparae, 45 minutes later, $\frac{1}{130}$ grain (0.5 mg.) of scopolamine, 45 minutes later, a dose of $\frac{1}{260}$ grain (0.24 mg.) of scopolamine, repeated again in 45 minutes and thereafter every 1 or 2 hours.

In a series of 755 cases, this proved to be a satisfactory combination for the production of seminarcois during the first stage of labor, providing a pleasing analgesia for the mother with little, if

any, effect on the baby. In some cases a small dose of 1 of the barbiturates was administered in conjunction with di-laudid-scopolamine analgesia. When ethylene or nitrous oxide was used for anesthesia in the second and third stages, apnea occurred in only 4.2 per cent of the babies. With ether, respiratory difficulty was encountered more frequently.

Oral Paraldehyde—L. H. Douglass, F. W. Peyton and J. R. S. Siau⁹ present the results of 300 additional patients receiving oral paraldehyde during labor.

In this series the paraldehyde was combined with aromatic elixir instead of the propylene glycol, alcohol, and syrup of acacia mixture, the result being that the total quantity to be swallowed was much smaller, nausea and vomiting were much less frequent and the taste was as effectively disguised. Elixir aromaticum U. S. P. (simple elixir) is a syrup almost universally used as an agent to improve the taste of liquid medicines; it is easy to procure, inexpensive and perfectly harmless.

Technic—It is no longer considered necessary to wait for any particular amount of cervical dilatation or descent of the presenting part before beginning analgesia, the desire of the patient for relief from pain being the main indication. She is told that she will be given something as soon as she wishes and is cautioned not to wait too long before seeking relief, otherwise it may be given too late for her to receive the full benefits. Better results are obtained when the paraldehyde is preceded by either $1\frac{1}{2}$ to 6 grains (0.1 to 0.39 Gm.) of pentobarbital sodium, the usual dose being 3 grains (0.194 Gm.), or $\frac{1}{6}$ to $\frac{1}{3}$ grain (0.01 to 0.02 Gm.) of pantopon, it being remembered that the 2 drugs should not be given in combination. Usually about 1 hour is allowed to

elapse after the preliminary medication before giving the paraldehyde mixture, although this is not absolutely necessary and may be disregarded if labor is progressing quite rapidly. The paraldehyde and aromatic elixir are given in equal parts, the amount ranging from 4 to 6 drams (16 to 24 cc.) each, the average being 5 drams (20 cc.), the dosage not varying with the age, size, or parity of the patient. The 2 are stirred briskly and the patient permitted to smell of the mixture or told that the odor and taste are pungent and slightly breath taking. The nostrils are loosely plugged with cotton and the patient is instructed to swallow the dose quickly; she is then given a few swallows of water and permitted to lie down and after a few minutes the cotton is removed from the nares.

If, as happens in a few cases, the patient is nauseated and regurgitates the mixture, an interval of about 15 minutes is allowed and the administration repeated. In attempting to decrease nausea it is helpful to have the patient breathe deeply. The paraldehyde, elixir, and glass used should be kept in the icebox, for chilling aids materially in eliminating the slight burning sensation and reduces the odor by decreasing the volatility of the paraldehyde.

The authors maintain that there are no contraindications to paraldehyde in labor, that expulsive efforts of the mother are not diminished or abolished; that complete amnesia is obtained in over 90 per cent of the cases, that oral paraldehyde does not prolong the duration of labor, and that there are no detrimental effects upon the mother.

There is a definite lowering of the blood pressure in hypertensive cases and the drug is recommended for the handling of pre-eclampsia and eclampsia.

There is no increase in postpartum bleeding. No fetal deaths in this series can be attributed to paraldehyde. It is perfectly safe, they claim, for use in the home.

E. D. Colvin and R. A. Bartholomew¹⁰ also report on improvements in the paraldehyde method of relief of pain in labor. A more dependable and complete amnesia may be obtained if paraldehyde is preceded 1 to 2 hours by 3 grains (0.194 Gm.) of nembutal, or 6 grains (0.39 Gm.) of sodium amytal. In this respect no change has been made in the technic. If rapid action is desired, the contents of the capsules dissolved in 1 ounce (30 cc.) of water may be given 20 to 30 minutes preceding paraldehyde.

The authors' method of administration of paraldehyde has been changed from rectal to oral in the great majority of cases. The principal reason for this change has been the occurrence, in several cases, of undoubted trauma to the upper rectum or lower sigmoid from the impact of the rectal tube in the attempt to inject the olive oil-paraldehyde solution sufficiently high to insure retention and rapid absorption. Even with the use of a fairly soft rectal tube and care in manipulation, trauma to the bowel wall may occur, as evidenced by tenesmus, localized pain and induration over the sigmoid and moderate fever, coming on 4 to 5 days after delivery. The condition has fortunately subsided within a few days but is nevertheless an unnecessary discomfort to the patient and worry to the attendant. The oral method is simpler, they claim, more easily intrusted to a nurse and is more rapid in action.

The authors have found that the great majority of patients willingly take paraldehyde by mouth, especially if they are already somewhat drowsy from the administration of nembutal or sodium amy-

tal during the preceding 1 or 2 hours. The initial dose of 6 drams (24 cc.) is stirred well in about 2 ounces (60 cc.) of cold water. The patient should be raised to a sitting position in bed. Not more than a swallow should be taken at first, followed by a small piece of orange. If vomiting occurs, due to dislike of the drug or to having taken food too recently, it will occur usually within 5 minutes and very little of the dose will thus be lost. The stomach then being empty, or if no vomiting has occurred within the 5 minutes, further swallows are taken at intervals of several minutes, until the entire dose has been taken within a period of 15 or 20 minutes. The patient begins to sleep and amnesia is already present by the time the last swallow has been taken.

Subsequent doses of 1 to 2 drams (4 to 8 cc.) may be necessary if vomiting occurs or if the behavior or conversation of the patient indicates returning consciousness. The total dose rarely exceeds 6 to 8 drams (24 to 30 cc.) of paraldehyde preceded by 3 grains (0.194 Gm.) of nembutal or 6 grains (0.39 Gm.) of sodium amytal. Should vomiting be persistent, it may then be necessary to administer paraldehyde in olive oil by rectal injection. To lessen the possibility of vomiting, it is well to caution the patient to eat very lightly, if at all, at the onset of labor.

With paraldehyde as a basic amnesic agent, using only a small dose of barbiturate, cases of exaggerated motor or psychic activity occur in only a small percentage of patients and may be controlled by a dose of morphine.

The authors have made frequent use of artificial rupture of the membranes just preceding the administration of paraldehyde or just after amnesia is fully established, to further insure efficient pains and good progress. This has proved to

be a helpful and harmless procedure, provided the head is fixed, the cervix thin and dilated 4 to 5 cm., and the pains occurring at 3- to 4-minute intervals.

In the majority of cases there is a spontaneous increase in the frequency and strength of the pains within 1 hour. If inertia persists beyond this period, several drops of pituitary extract should be instilled onto the nasal mucous membrane, using a hypodermic syringe as a dropper. This is preferable to plugging the nostril with cotton saturated with pituitary extract, as it is less likely to irritate or arouse the patient. There is a definite effect within 5 to 10 minutes, but one practically never encounters the severe type of reaction, with prolonged tonic contraction and slowing of the fetal heart sounds that is likely to occur with the subcutaneous administration.

Analysis of the last 500 consecutive cases in which paraldehyde was used shows that complete amnesia was obtained in 92.6 per cent and partial amnesia in 6.2 per cent.

The average duration of amnesia before delivery was 5 hours 24 minutes in nulliparas and 3 hours 18 minutes in multiparas. The average duration of sleep after delivery was 4 hours 48 minutes in nulliparas and 5 hours 36 minutes in multiparas. The hours of sleep during and after labor account for the feeling of rest and well-being so frequently noticed when these patients react.

Control of the patient for final cleansing, draping and delivery is greatly facilitated by the induction of light primary ether anesthesia during crowning of the head, just before moving the patient to the delivery room. A mild degree of apnea or sluggishness in breathing or crying is to be expected in about 12 per cent of full-term, normal babies but is of no serious significance and is easily over-

come. If paraldehyde is given in premature labors, coramine should be given to induce more prompt and thorough expansion of the lungs.

J. Kotz, G. B. Roth and W. A. Ryon¹¹ discuss the value of paraldehyde analgesia. The authors have found that paraldehyde is an efficient obstetric analgesia-anesthesia producing agent with a low toxicity and that when failures have occurred they have usually been due to insufficient dosage or improper technic. Toxic effects have rarely occurred, and these have appeared when the patient had an idiosyncrasy to the drug.

In the fatal case reported in this paper there was unusual susceptibility to paraldehyde. The hypersusceptibility was regarded as being probably produced by a pathologic condition in the patient, which was not discovered until necropsy, in this instance death occurring after 1 ounce (31 cc.) of paraldehyde was given by rectum as a single dose in the beginning of labor.

Since January, 1935, they have used paraldehyde in more than 600 labor cases with very gratifying results. It is an effective analgesic which is relatively quite safe. They believe that its use should not be discontinued because of their 1 fatality incident to its administration, an event which might occur with any drug to which a patient is hypersusceptible. Such hypersusceptibility to paraldehyde seems to be quite rare. It is best, however, that the use of paraldehyde should be limited to hospital patients since the patient under its influence requires special care, particularly during labor.

CHORIONEPITHELIOMA

Diagnosis—It has been demonstrated that large quantities of gonadotropic hormones are excreted into the urine when chorionepithelioma or hydatidiform mole

is present. It has been shown that up to 50 per cent of the chorionepitheliomas studied have been preceded by hydatidiform moles. It would be advantageous, therefore, if a diagnosis could be made early by testing the urine for these hormones. It has been contended that if a diagnosis was made before full clinical signs developed, complete eradication of the tumor could be carried out before metastasis occurred.

A. J. Kobak¹² warns, however, that the presence of urinary gonadotropic hormones in high concentrations necessitates the definite exclusion of a normal pregnancy before the diagnosis of hydatidiform mole or chorionepithelioma is considered.

DIAGNOSIS OF PREGNANCY

Early Diagnosis With Spectroscope

A new spectroscopic method for the early diagnosis of pregnancy is reported by J. Samuels.¹³ In the pregnant woman the oxyhemoglobin reduction time, taken daily, remains constant, because the cyclic oscillations of menstruation and ovulation do not occur. A constant figure on 4 or 5 successive days is sufficient to establish the diagnosis of pregnancy.

If impregnation occurs with the first ovulation, in a woman with a menstrual cycle of 31 days, the diagnosis can be established by the eighth or ninth day of the cycle, i. e., 7 or 8 days after impregnation and about 12 days before menstruation would be due. With a 28-day cycle, pregnancy can be diagnosed 9 or 10 days before the date when menstruation would be expected. If fertilization took place with the second ovulation, the diagnosis of pregnancy can be established after 6 or 7 days.

Pregnancy Biologic Tests

Experiences with the biological tests for pregnancy are discussed by A. Mek-

ler.¹⁴ This investigator's report is based on 1360 hormone pregnancy reactions that were carried out at the woman's clinic of the University of Zurich in the years 1930 to 1935 inclusive. In 676 cases the mouse test of Aschheim-Zondek was used and in 684 the rabbit test of Friedman. It was found that the reliability of the mouse test was 96.6 per cent, that of the rabbit test 93.1 per cent. If the doubtful reactions are disregarded, the figures are 97.8 and 97.4 per cent, respectively.

The reaction gives positive results a few days after the first missed menstruation and produces reliable results as early as 8 days after the first menstrual omission. In cases of abortion and extrauterine pregnancy, it was observed that the disappearance of the positive reaction is dependent on the clinical symptoms. The more severe the clinical symptoms of the abortion or the extrauterine pregnancy, the sooner does the reaction become negative, however, the more subdued the clinical aspects, the longer does the positive reaction persist.

The 3 degrees of the anterior pituitary hormone reaction as distinguished by Aschheim and Zondek are: Reaction I, the presence of large, ripe follicles with extensive cavity formation, reaction II, the presence of blood-filled, ripe follicles, blood dots, and reaction III, the presence of corpora lutea, which enclose the ovum, corpora lutea atretica. Zondek and Aschheim demanded reaction II or III for a definite diagnosis of pregnancy, because they observed reaction I also in some cases in which pregnancy was absent. Mekler thinks that during the early period of pregnancy reaction I may be taken as an indication of pregnancy in a woman with normal genitalia and when tumor, severe endocrine disturbances and the preclimacteric can be ruled out. In extrauterine pregnancy, reaction I is of

such frequent occurrence that together with the clinical aspects it is of considerable diagnostic value. Reaction I is to be regarded as an intermediate reaction in case of transition from negative to positive (early pregnancy) and from positive to negative (abortion, dead fetus, extra-uterine pregnancy).

In the rabbit method, however, the rupture of the follicle does not have the significance of a transitional reaction, because in rabbits a spontaneous rupture of the follicle is possible. A comparison of the mouse test and of the rabbit test suggests that it is best to use both types of animals for the diagnosis of pregnancy: In the earliest stages of pregnancy and in the observation of the disappearing symptoms of pregnancy, the mouse test is better, because reaction I can be utilized; however, for greater rapidity of the diagnosis of pregnancy the rabbit test is advisable

Aschheim-Zondek Reaction and Hormone Titration

The quantitative method of anterior pituitary sex hormone determination is discussed by A. Brindeau, H. Hinglais and M. Hinglais.¹⁵ These investigators find a remarkably constant relation between the hormone content of the blood and the vitality of the syncytial elements of the placenta. This relation is so regular that from the practical point of view the gonadotropic hormone content of the blood can be considered as proof of the activity of the placental organ. The authors insist that it is the vitality and not the quantity of the active placental tissue which is important.

The quantitative method described, that is, the hormone titration of the serum, consists in the determination of the gonadotropic substance in the serum of the patient. The titration is performed

on the rabbit and the unit is defined as the quantity of gonadotropic substance which, when injected intravenously, suffices to elicit within 48 hours in a rabbit weighing about 2 kg. at least 1 hemorrhagic dot in 1 of the 2 ovaries. The result is expressed in a rabbit unit per liter of serum; that is, as a number directly proportional to the quantity of the hormone secretion. They say that the secretion of gonadotropic substance during pregnancy as determined in the blood is always abundant. Expressed in rabbit units per liter, the lowest values are between 1000 and 2000 and the highest between 20,000 and 25,000. During the first third of the period of pregnancy, the values are between 10,000 and 12,000 units; this figure decreases during the last third of pregnancy. The extremes of the aforementioned figures define the limits of placental activity compatible with a normal pregnancy. If less than 2000 units is present, the existing pregnancy is accompanied by a placental hypoactivity and spontaneous abortion threatens. If less than 500 units is detected, death of the ovum may be regarded as certain. If more than 25,000 units is present, the pregnancy is accompanied by a placental hyperactivity.

In certain toxicoses of pregnancy, such as hyperemesis gravidarum, the hormone content of the blood may be between 25,000 and 50,000 units. In pathologic evolution of the ovum, such as vesicular mole, the hormone content may be 60,000 units or more. In order to detect the development of a malignant chorioneplithelioma following the expulsion of a vesicular mole, it is necessary to repeat the titration of the hormone content of the blood at definite intervals, after 8, 20, 30 days, and so on. If the hormone content decreases to zero, the woman may be regarded as out of danger, but if the

hormone content increases again after having been decreased, malignant degeneration is certain.

GONORRHEAL OPHTHALMIA NEONATORUM

A. J. Skeel¹⁶ reports the procedure employed in over 10,000 successive cases in which gonorrheal ophthalmia was totally eliminated. In the last 3000 deliveries the patient has been given every 12 hours during labor prophylactic vaginal injections of an aqueous solution of *merthiolate*, 2 parts of distilled water to 1 part of merthiolate solution. This was done with no thought of gonorrheal infection but may have offered some protection.

At the St. Luke's Hospital in Cleveland, the routine procedure is as follows:

1. At the time of delivery of the head, the eyes are carefully cleansed with dry sterile sponges. No boric acid solution is used.

2. When the cord has been cut, 3 or 4 drops of 0.5 per cent solution of *silver nitrate* are instilled and the lids are gently manipulated to distribute the solution to every part of the conjunctival sac. After 45 seconds the sac is freely flushed with a 20 per cent solution of *mild silver protein*. This irrigation is repeated on 3 successive days as a routine part of the nursery technic. The substance must be completely dissolved. The solution is prepared twice weekly.

The author thinks that the repeated conjunctival flushing with a bland silver preparation is vital to the success of the method. The rationale of this technic is as follows:

1. Irrigation with a boric acid solution is not used; this solution is not a gonococcicide, and its use serves merely to introduce the organisms into the conjunctival sac.

2. He believes that the occasional late infection which was observed before the use of repeated irrigations with bland silver solution occurred as the result of the presence of a few organisms of reduced virulence, which are destroyed by the successive treatments.

HEMOPTYSIS IN MALIGNANT HYDATID MOLE

E. R. Pund, R. B. Greenblatt, and C. Thompson¹⁷ discuss the importance of hemoptysis in malignant hydatid mole. In a case of invasive mole, hemoptysis was a prominent feature. Roentgen studies of the chest revealed metastatic foci in the lungs. Following hysterectomy and without radiation therapy, the metastatic pulmonary foci regressed and the patient recovered. The biologic hormone assay for gonadotropic substance in the urine was only 5000 mouse units per liter before hysterectomy and 150 mouse units per liter 3 weeks after operation. These low hormonal values were in harmony with the regressive features of the neoplasm and were indicative of a hopeful prognosis. The hemoptyses in such cases are due to pulmonary deportation of villi or syncytial cell masses with transitory proliferation rather than true metastases. The authors believe that removal of the primary focus, *i. e.*, hysterectomy, should always be performed regardless of the seeming hopelessness of the situation.

PARTURITION

Cervical Dilating Bag

E. G. Waters¹⁸ discusses the use, abuse and hazards with the employment of the Voorhees bag in obstetrics as gleaned from a study of 372 cases occurring in 25,969 parturitions at the Mar-

garet Hague Maternity Hospital (an incidence of 1.4 per cent).

Well-recognized indications, such as placenta previa, pre-eclampsic toxemia, abruptio placentae, primary uterine inertia, nephritis and heart disease, account for over 70 per cent of the total.

The author believes that the Voorhees bag is too valuable to be either disregarded or misused. The purpose of a bag is to stimulate either the uterus to contraction through irritation of the lower uterine segment and effect cervical dilatation and effacement, or to cause these, plus tamponade, to check hemorrhage in placenta previa. It may occasionally be used to retain a replaced prolapsed cord. It is most useful at term, with the cervix softened and partly effaced and least valuable earlier in pregnancy when the cervix is long and tight. The bag must fit the cervix, and while small bags are attended by a greater likelihood of long labor or failure, there is less risk of prolapsed cord or displacement of presenting part. If the membranes are intact, it must always be placed extraovularly, except in placenta previa. With the exception of placenta previa, the size of the bag chosen depends upon the indication, the part presenting and the condition of the cervix, although No. 4 and No. 5 give the best results in general. No traction is used except in placenta previa, unless the bag tends to slip upward. The bag must be filled until the stem is tense, for if partly filled it will slip into the vagina. In placenta previa, the largest bags that can be safely introduced are ones that most effectively tampon the bleeding.

Since labor ensues early and with stronger pains than usual, the progress of the bag must be checked constantly by rectal examinations, and abdominal examinations made for change in uterine tension and fetal position. As soon as the bag is through the cervix, its function

is completed and it is removed. A vaginal examination must be made immediately to look for prolapse of cord and malpresentation, the 2 most frequent causes of stillbirths. Either complication compels prompt delivery if the cervix is completely effaced and dilated or easily dilatable. Hemorrhage from placenta previa after bag expulsion likewise forces prompt action, and version tamponade is the usual procedure of election. If the uterine contractions cease with the expulsion of the bag, hypodermic pitocin in 1 to 3 minim doses at half hour intervals is indicated, none are given after resumption of pains, and larger doses are absolutely prohibited. If conditions are favorable, expectant observation should take precedence over operative manipulations, with their high morbidity and fetal mortality.

A proper technic permits introduction without anesthesia, an important actuality in view of imperative anesthesia accompanying the nearly 50 per cent operative incidence subsequent to bagging.

Labor in Elderly Primiparae

C. R. Tew and K. Kuder¹⁹ call attention to the widespread impression entertained by both the laity and the profession that elderly primiparae are more prone to the serious complications of labor and pregnancy. The authors show, by the use of clinic material, that these apprehensions are in some measure well founded by actual obstetric experience and not "tradition" as it has been so often called. Their conclusions are the following:

There is a marked increase in the incidence of toxemias, particularly the more serious types of placenta previa and myoma uteri. The operative incidence is at least double that of the ordinary clinic population. The infantile mortality is markedly elevated. The maternal mor-

tality is 4 times greater than the clinic population. Labor is definitely prolonged and morbidity and puerperal infection rates are significantly increased.

The incidence of elderly primiparae (35 years of age and over) was 2.01 per cent in a series of 11,919 obstetric patients. Although there is a marked difference in the total incidence of all types of contracted pelvis in this group of women, funnel pelvis are definitely more predominant than among younger primiparae.

Among the complications of labor in elderly primiparae, the authors note an increased incidence of occipitoposterior positions, arrested transverse positions, and postpartum hemorrhage. The head of the child is unengaged at term in 53.3 per cent of elderly primiparae, as compared with a figure of only 20.9 per cent in a control series of patients.

The authors conclude that "elderly primiparae," *per se*, does not constitute an indication for cesarean section, unless there is an accompanying complication which still further adds to the risk to the offspring.

Cesarean Section

Transperitoneal Exclusion—Technic—In an effort to attain as closely as possible the margin of safety that the Latzko operation gives and also to secure the advantages of the transverse low segment operation, the following technic of a modification of the original Frank operation is described by I. F. Frost.²⁰

This operation presents no great technical difficulties as its technic is practically that of the low transverse segment operation.

The Pfannenstiel incision gives adequate room and exposure and brings the incision directly over the uterovesical fold of peritoneum. By doubly suturing the peritoneal layers, the abdominal cav-

ity is sealed above and below. This allows the uterine incision to be placed entirely in the lower segment, entirely covered by peritoneum. It provides for the natural point of drainage into the cervix, and adds to the usefulness of the transverse low segment operation by rendering it more safe through the exclusion of the abdomen if desired. It is not contraindicated in placenta previa.

The technic of the operation is described in steps.

Step 1. The anesthesia may be general, spinal or local. Local anesthesia is preferable in toxic cases. Two per cent novocain is used in the skin and 1 per cent novocain in the peritoneum and uterus. A basal anesthetic should be given prior to the local anesthesia. Nembutal, $4\frac{1}{2}$ grains (0.29 Gm.), gives good results.

The patient is catheterized, preferably in the operating room, to insure complete emptying of the bladder.

Step 2. At the level of the anterior-superior spines, a Pfannenstiel incision $4\frac{1}{2}$ inches (11.2 cm.) in length is made. The fascia is separated from the muscles both upwards and downwards to insure plenty of fascial retraction. The muscles are divided in the midline and separated, exposing the peritoneum. The peritoneum is opened transversely to a point sufficient to expose the uterus adequately.

Step 3. The uterovesical fold of peritoneum at its loose attachment is now picked up with plain forceps and injected both to the right and to the left with 1 per cent novocain, if local anesthesia is being used, or sterile saline solution in case of spinal or general anesthesia. A long wheal of peritoneum will be raised. This is incised with scissors, leaving a sufficient margin of peritoneum both above and below for suturing purposes. The bladder is now dissected away from the anterior surface of the uterus for a

distance of about 2 inches (5 cm.), thus exposing the lower segment.

Step 4. The upper parietal peritoneum is now doubly sutured to the upper portion of the visceral peritoneal flap, using a No. 1 chromic intestinal suture. This suture starts from one end of the peritoneum and is carried to the opposite side. A reinforcing suture with invagination of the peritoneum is now applied. The lower edges of parietal and visceral peritoneum are sutured in the same manner, and are joined at either end of the first line of suture, thus entirely shutting off the abdominal cavity. A Doyen retractor is placed in the lower angle of the wound and the lower segment is exposed. A strip of 2-inch iodoform gauze is placed across the upper sutured layer of peritoneum to protect this area from the excess of the uterine spill.

Step 5. A small transverse incision is made in the lower segment and the suction tube is introduced, removing as much amniotic fluid as possible. The incision is now enlarged transversely by means of bandage scissors, gently curving the incision upwards at either end, while T clamps are applied as the incision is made. A small vertical incision at the midpoint of the transverse incision will give added room if necessary. As the incision is made, 8 minims ($\frac{1}{2}$ cc) of pituitin is injected into the uterus, and a hyperdermic injection of ergotrate is given intramuscularly.

The child is delivered by inserting the hand carefully under the lower flap and raising the presenting part, at the same time exerting pressure on the fundus. The blade of a forcep used as a shoehorn will also aid the delivery, as will the application of small forceps. The placenta generally will become detached as the uterus contracts.

Two Kocher forceps placed at either angle of the wound will insure proper

approximation of the edges. Interrupted sutures are placed and second row of continuous No. 2 chromic is added.

Drainage of the retrovesicular area is optional, but, if desired, it may be established according to the method suggested by DeLee or that of Aldridge in his modified Latzko operation. A small cigarette drain is placed between the bladder and the lower uterine segment. This drain passes out through the mid-portion of the uterine incision where it is sutured by No. 0 catgut. The lower end is carried out into the vagina. It is allowed to remain for 7 days and is removed through the vagina.

Step 6. The lower reflected flap of the sutured visceral parietal peritoneum is now carried up and sutured to the upper united visceral parietal layer, by a few interrupted catgut sutures.

Step 7. The muscles are now allowed to fall together in the midline and may be approximated by 1 or 2 loose catgut sutures. The fascia is grasped at either end by skin hooks or Kocher artery forceps and a running No. 3 kaldernic suture is started through the skin at one end and carried through the fascia as a running mattress suture, emerging at the opposite end from the skin. When this suture is pulled taut, it snugly approximates the fascial edges. A similar suture is placed starting through the skin as before, but below the first. This includes the superficial fascia and again emerges from the skin below the point of the first emerging suture. After the skin is closed, the 2 suture ends at either end of the wound are tied over a gauze roll. The sutures are removed by cutting both at one end, iodinating them and drawing them out 12 days later. It is better to cut them on the tenth day, and remove them on the twelfth day. The sutures may also be cut off at either end, allowing the ends to retract into the wound and remain.

This will give added strength to the wound.

Cullen's Sign—E. A. Gerrard²¹ points to the diagnostic value of Cullen's sign in a case of antepartum rupture of a cesarean section scar. He cites the case of a patient who 3 years previously had been delivered for the first time by cesarean section of the upper segment after an extended trial of labor. The child was stillborn and the puerperium was difficult. Her present pregnancy had been uneventful up to the thirty-sixth week, when she began to feel pain in the lower part of the abdomen. Two days previous to the author's seeing her she had had an attack of acute cutting pain which lasted for about 4 hours. Shortly afterward she noticed a reddish stain at the umbilicus. There had been no vomiting, and as she walked into the clinic for her fortnightly antepartum examination her only complaint was of a slight feeling of soreness. On examination, her general condition was found to be excellent. The umbilicus showed a reddish purple stain about the size of a shilling. On palpation the child was found to be lying in a left sacroanterior position.

Despite the patient's excellent condition, the presence of Cullen's sign was deemed to indicate intraperitoneal hemorrhage, and a diagnosis of a ruptured cesarean scar was made. The abdomen was opened through a right paramedian incision. On retraction of the rectus the peritoneum in the umbilical region was seen to be infiltrated with blood. Incision of this structure revealed no free blood in the peritoneal cavity, but a clot of blood about 2 inches long and 1 inch broad was found attached to the old uterine scar. The clot was removed, exposing a tear about 1 inch long which had been effectively plugged by the placenta, which was lying immediately be-

neath it. The site of rupture was extended upward and downward and the child was removed. It breathed a moment or two later. There was profuse hemorrhage, but the uterus retracted well after the placenta was removed and an injection of solution of posterior pituitary and ergometrine was given. The author is inclined to think that in his case there must have been damage to the peritoneum at the time of rupture of the uterine scar due to the clot of blood and the attachment of the placenta to the anterior wall of the uterus.

Placenta

Transfer of Sulfanilamide—In order to determine the transfer of sulfanilamide through the placenta, R. H. Barker²² analyzed samples of maternal venous blood (from 17 pregnant women suffering from infectious diseases who had received the drug shortly before delivery) and of umbilical vein blood for free sulfanilamide content, according to the method of Marshall. He found that sulfanilamide given orally to the mother in labor is found in almost equal concentrations in maternal and fetal venous bloods. Apparently the placenta is freely permeable to the drug, and fetal complications from excessive maternal dosage are theoretically possible. No complications occurred in any of the infants of this group. The doses administered, however, were small in comparison with those that would be necessary in the treatment of the severe maternal infections.

Placental Blood—At St. Mary's Hospital, Montreal, Quebec, J. R. Goodall, F. O. Anderson, G. T. Altimas and F. L. MacPhail²³ have made a practice of collecting and storing fetal blood for transfusion as needed. In the course of a great many transfusions there has not been 1 untoward reaction, not a single rise of temperature attributable

to transfusion. When transfused, the fetal blood is heated in a basin of water and shaken. It should be filtered through 2 layers of sterile gauze.

Advantages of Fetal Blood—The advantages of the preserved fetal blood are (a) it contains from 20 to 35 per cent more coagulation power than adult blood—probably nature's provision to prevent exsanguination of the newborn in animals, and (b) food and other extraneous allergic reactions are eliminated, because the unsplit proteins present during digestion are autodigested within 48 hours in preserved blood.

The preservative used by the Moscow (U. S. S. R.) Institute of Haematology was employed. It consists of the following ingredients, made up according to the following formula:

Sodium chloride	70 Gm
Sodium citrate	50 Gm
Potassium chloride	02 Gm
Magnesium sulfate	0.004 Gm
Bi-distilled water	1000 cc

Now available in 25 cc. ampoules, which are mixed with 100 cc of distilled water, the preservative and the blood from each patient are mixed in equal proportions. There is on the average 125 cc of fetal blood available at childbirth. (The amount may vary from 100 to 150 cc.)

The technic of collecting the blood is as follows:

When a baby is born, it is laid upon the mother's abdomen. The cord is tied or clamped and wiped clean with a sponge moistened with 75 per cent alcohol. The cord is stripped free of blood for about 6 inches and cut with sterile scissors.

To prevent contamination of the cord and receptacle by any fluid extraneous to that under collection, a special towel with a 2-inch hole in the center is put over the hand, holding the cord in such a manner that the hand is opposite the

hole. The end of the cord is passed through the hole in the towel.

With an Allis forceps, the towel is clamped to the operator's gown near the elbow. The end of the cord is then passed through the hole in the towel and directed into the funnel of the collection receptacle held by a nurse. Pressure on the cord is then released completely and the blood collected. Pressure on the fundus hastens emptying of the placenta. When completed, the cord is clamped.

Preparation of Receptacle—Through the funnel, the blood runs into a wide-mouthed glass flask of 300 cc capacity. Before using, the flask and the glass funnel are thoroughly cleansed and rinsed several times with distilled water. An ampoule of preservative and 100 cc of distilled water are placed in each flask and corked with a stopper of absorbent cotton. Flask and funnel are wrapped separately in a cloth and sterilized in the autoclave. When cool, they are ready for use.

When the blood is being collected, the funnel is partially released from its cover and handed aseptically to the surgeon. The flask covering is released from the bottom so that when the nurse holds the flask by the base, the cloth falls over her hand. The surgeon places the funnel in the flask and the nurse holds these in position for receiving the blood.

When the collection is finished, a few drops of blood from the end of the cord are taken in test tubes; 1 for grouping, the other for a Wassermann test. These flasks are stored in a refrigerator with a temperature between 33° and 38° F. (0.6° and 3.3° C.). Temporary changes of this temperature do not affect the character of the blood. It is ready for transfusion as soon as grouping and Wassermann reaction tests are reported.

Placental blood is not collected in cases of obvious transmissible disease in either mother or child. It should not be taken from cases in which the membranes have ruptured for more than 48 hours before delivery, nor in cases of definite prematurity. In cases of marked asphyxia pallida, the amount of blood obtained is so small that it is worthless. Eclampsia, however, is not a contraindication for the collection of placental blood.

R. Keller and J. Limpach,²⁴ report on the use of placental blood for transfusion purposes before and after gynecologic operations. Placental blood has a high content in erythrocytes, leukocytes and hemoglobin. Of course, the placental blood should be derived from healthy parturient women. After the child is born, the umbilical cord is grasped with a sterile forceps, cut and carefully disinfected. The first few drops of blood are placed in a test tube containing a solution of potassium oxalate (potassium oxalate, sodium chloride and water). This mixture is centrifuged and conserved to test the compatibility. Then the placental blood is collected in a glass container, previously rinsed with 5 cc of a 10 per cent solution of sodium citrate. While the blood is flowing, the container is shaken mildly. The average amount of placental blood obtained after each delivery is from 60 to 90 Gm.

The blood is stored at a temperature of 2° C and is utilized within 36 hours. From 4 to 5 cc of blood is withdrawn from the patient who is to receive the transfusion. Following centrifugation, 2 drops of the serum of the recipient is mixed with 1 drop of the donor's blood that had been collected in the test tube with the sodium citrate. The mixture is observed for from 5 to 10 minutes and the macroscopic observation is followed by microscopic control. If there is no

sign of agglutination, the transfusion can be made. The container with the blood is filtered through 3 thicknesses of sterile gauze into a graduated cylinder that has been rinsed with physiologic solution. Then the blood is introduced into the vein of the recipient. This method of indirect transfusion has proved entirely satisfactory.

PREGNANCY

Physiology—A case in which the corpus luteum of pregnancy was removed on the fifty-eighth day after the last menstrual period is reported by H. W. Jones, and P. G. Weil;²⁵ abortion did not take place. In the human being it is known that there are large amounts of pregnanediol, and therefore progesterone, all through pregnancy. Its discovery after the removal of the corpus luteum of pregnancy, as in the case reported in this paper, would seem to clinch the fact that progesterone is produced late in pregnancy by some other organ than the corpus luteum. The fact that pregnanediol disappears from the urine within 24 to 48 hours of delivery would suggest that the site of its production is the placenta.

On the other hand, the authors found that, in the case reported, no pregnanediol was present in the urine for about 12 days after the removal of the corpus luteum. It then reappeared in increasing amounts. This would indicate that in the human being pregnancy can survive after the withdrawal of progesterone, or that it can survive on amounts too minute to be determined by the method employed.

Progesterone, it appears, is produced early in pregnancy chiefly by the corpus luteum and this is supplemented later by a supply from the placenta. It is probable that the corpus luteum can be removed without untoward effects on the

pregnancy after the placenta has begun its production of progesterone and that the beginning of its production varies from case to case.

The period of excretion of the compound pregnanediol, an excretion product of progesterone, was found to be from 3 to 12 days and the amount of the compound, for an entire cycle, from 3 to 54 mg. In 9 cases of normal pregnancy, up to the sixtieth day counting from the first day of the last menstrual period, J. S. L. Browne, J. S. Henry and E. M. Venning,²⁶ found from 4 to 10 mg. during 24 hours. From this level, which is comparable to that in normal menstruation, the rate of excretion begins to rise, reaching 40 mg. by the one hundred and fiftieth day. The peak of excretion is reached in the eighth month, when in 2 cases 80 and 73 mg. in 24 hours was excreted. Within 24 hours of delivery the compound completely disappears from the urine.

Calcium Requirements—A timely and conservative editorial on the calcium needs during pregnancy is presented by H. J. Stander.²⁷ Many unwarranted claims for calcium, phosphorus, and vitamin therapy, the author points out, have been advanced.

It is well established that the normal adult requires a minimum of 7 grains (0.45 Gm.) and an optimum of about 11 grains (0.7 Gm.) of calcium a day. During the last trimester of pregnancy the calcium requirements are increased to probably about 23 grains (1.5 Gm.) per day. Absorption of calcium, in the form of soluble salts, which are formed only in an acid medium, occurs in the small intestines. In order to accomplish this, calcium may be taken in the form of milk at meals, or as calcium salts no nearer meals than 4 hours after and 1 hour before. Furthermore, should there

be no exposure to sunlight, vitamin D is essential to its utilization.

Calcium therapy undoubtedly relieves the muscular cramps that may occur during pregnancy. However, there is no evidence to assume that calcium administration prevents dental caries, a condition for the prevention and cure of which we must still rely on proper dental hygiene and care. Furthermore, there is some evidence to show that too much calcium and vitamin D may lead to early calcification in the fetal bones (osteosclerosis). As to the calcification of the teeth of the offspring, this is postnatal and does not depend on the ingestion, in addition to an adequate diet, of calcium and phosphorus by the mother.

It may be claimed safely that during pregnancy all calcium and phosphorus requirements are supplied by an adequate diet containing these elements as well as the other dietary essentials. Certainly, any deficiency in these 2 elements in the diet may be corrected by the addition of milk, an easily assimilable source of these substances. The practice of instructing all pregnant patients to take 1 quart of milk a day, especially during the last 2 trimesters of gestation, appears to Stander to be sound and to meet all requirements for calcium and phosphorus. Overtreatment may be as injurious as the deficiency itself.

Estrogen Metabolism—Estradiol or dehydrotheelin $C_{18}H_{24}O_2$ is in all likelihood the primary ovarian estrogen. The work of G. Pincus and P. A. Zahl,²⁸ on rabbits indicates that estradiol is converted into estrone ($C_{18}H_{22}O_2$) and that this reaction is reversible—chemical evidence also demonstrates the reversible nature of the estradiol to estrone conversion; that estrone is converted into estriol $C_{18}H_{26}O_3$ when the uterus is present and under ovarian control, this conversion being irreversible and greatly

facilitated by luteal secretion; and that progestin partially protects these 3 estrogens against destruction, thus permitting both utilization and excretion, there probably being no renal threshold.

Relatively high levels of estriol excretion, then, during what was presumable the luteal phase of the cycle suggest that in women, as in rabbits, *excretion of estriol* may be taken as a gauge of secretion of progestin. Thus would the marked drop in estriol 2 days before menstruation signify regression of the corpus luteum. This interpretation is strengthened by the work of E. H. Venning and J. S. L. Browne, who find that pregnandiol glucuronide, the excretion product of progestin, disappears from the urine 1 to 3 days before the beginning of flow. With the onset of menstruation there was a further drop in estriol and a rise in the potency of the estrone portion, so that the ratio of estrone to estriol during the first 2 days was much higher than at any other time in the cycle.

G. V. Smith, O. W. Smith and G. Pincus,²⁹ made a determination of the urinary estrone and estriol throughout pregnancy; from the time of the second missed period excretion of estriol increased at a more rapid rate than that of estrone, resulting in constantly higher ratios of estriol to estrone. In the urine of pregnancy, J. S. L. Browne, J. S. Henry and E. H. Venning²⁰ have quantitated pregnandiol glucuronide and have found a constant increase of this excretion product of progestin with advancing gestation, this indicating progressively greater secretion of progestin. Here again, as in the menstrual cycle, urinary estriol is apparently a gauge of the amount of progestin. Preceding delivery estriol excretion dropped off markedly, and there was a concurrent augmentation of the potency of the estrone fraction, which comparison of colorimetric

assay with bioassay indicated was due to some estrogen other than estrone. These findings, analogous to those at menstruation, suggest that in the *initiation of labor*, as in the initiation of *menstruation*, progestin deficiency in the presence of estrogen production may result in a changed metabolism of estrogens and the consequent action of a positive precipitating factor.

G. V. Smith and O. W. Smith³⁰ confirm this work on the female. Their studies indicate that:

1. Estradiol is convertible into estrone and estrone into estradiol.

2. Progestin, acting through the uterus (probably the endometrium), brings about the conversion of estrone to estriol, thus carrying the estradiol to estrone reaction to the right. Accordingly, the distribution of the estrogens in the urine supplies an index of progestin activity.

3. Progestin partially protects the estrogens against destruction, thereby allowing greater utilization and excretion. The amount of estrogen in the urine represents the balance between production and destruction.

4. Deficiency of progestin, therefore, results in (a) reduced conversion of estrone to estriol, (b) thus causing the estradiol to estrone reaction to swing to the left, and (c) greater destruction of all estrogens.

Clinically the determination of these investigators indicate that:

1. Endometrial bleeding is associated with both increased production and increased destruction of estrogen, which processes accompany a state of progestin deficiency, and that this situation is exaggerated in dysfunctional flowing.

2. The manifestations of pre-eclampsia coincide with changes in the urinary values for pregnandiol, estrone, estriol, and estradiol which reflect a progestin-deficient metabolism of the estrogens.

Complications in Pregnancy

Anemia—Treatment—Hypochromic anemia in pregnancy states T. M. Caf-faratto,³¹ may be prevented by the administration of small doses of *iron* with the ordinary diet or a diet which contains a sufficient quantity of iron to supply the patient with a daily amount of about $\frac{5}{8}$ grain (0.04 Gm.). The preventive treatment should be administered from the fourth month of pregnancy up to its completion. In hypochromic anemia it is advisable to give iron in large doses and a diet rich in iron but well balanced in proteins, fats and carbohydrates. The following daily doses of iron are in general use: from $\frac{1}{2}$ to $2\frac{1}{2}$ drams (2 to 10 Gm.) of iron and ammonium citrate, 30 to 45 grains (2 to 3 Gm.) of iron protoxalate or 6 to 25 grains (0.6 to 1.6 Gm.) of iron hydrochloride. A diet with predominance of proteins over carbohydrates and fats lowers the amount of hemoglobin, which remains unchanged when fats are in predominance and increases when carbohydrates predominate. The variations for assimilation of iron from food depend on the quality of iron and on the individual capacity of absorption. Iron contained in carbohydrates is more easily assimilated than that of fats and proteins.

Diabetes—E. Brandstrup and H. Okkels³² present 22 cases of pregnancy in 19 diabetic patients observed in the Lying-in Department A, Rigshospital, Copenhagen. This material is not suggestive of any change in the diabetic condition of the mothers during pregnancy. The restitution of these patients after the puerperium indicates that such changes as have been observed during pregnancy (frequency of acidosis and changes in the insulin requirement) are attributable to factors of a nature that does not directly concern the diabetic

condition. The obstetric risk is somewhat increased through a tendency to hydramnios, excessive size of the child and, especially, infection in the presence of eczema of the vulva. In the 22 cases observed, only 10 living children were discharged from the hospital. The great mortality among children of diabetic patients may probably be attributed to maternal hyperglycemia and acidosis. In 3 of the dead children the necropsy was extended to include a thorough microscopic examination of the endocrine organs.

The pathologic changes observed in the pancreas, hypophysis and thyroid are described. Commenting on these changes, the authors say that the maternal hyperglycemia alone brings about the pathologic changes in the child. In the discussion of the therapeutic problems, it is pointed out that in the future the main task of the treatment should be to employ such dietetic and medicinal measures as to make obstetric operations unnecessary. The pregnant diabetic patient must be watched closely, and the efforts must be aimed at the avoidance of hyperglycemia and acidosis. The therapeutic significance of protamine zinc insulin is emphasized.

Obesity—Pregnancy complicated by obesity, according to H. B. Matthews and M. Der Brucke,³³ calls for constant vigilance. Various degrees of toxemia, malposition and malpresentation, prolonged labor, uterine inertia, exhaustion, postpartum hemorrhage, increased maternal morbidity and mortality and increased fetal mortality are apt to be present. The author suggests the following measures:

1. The women should be seen early and often in their pregnancy.

2. Even though there may be no objective or subjective sign or symptom of toxemia, they should be treated as

already having mild toxemia. Their diet, exercises and personal hygiene should be closely scrutinized and carefully planned and carried out.

3. When possible, malposition or malpresentation should be corrected before labor begins.

4. It is frequently advisable to supplement the clinical diagnosis of position, presentation and size of the fetus and of the pelvic measurements with complete x-ray examination

5. In cases of unremitting toxemia, the fetus should be delivered as soon as compatible with fetal life, medical induction being indicated whenever possible.

6. When malposition and malpresentation further complicate the picture, prolonged labor with uterine inertia, maternal exhaustion and increased fetal distress usually supervene and are not infrequently followed by postpartum hemorrhage. A reasonable test of labor should be given, and if there is no progress, cesarean section should be performed.

7. When the obstetrician is finished, the obese woman should be referred to the internist for continued observation, since she presents many pathologic lesions of prime importance.

Psychosis—A timely discussion of psychoses complicating pregnancy which occurs in 1 in 858 pregnancies is presented by P. Piker.³⁴ The percentage incidence may be higher than 0.1 per cent for, in addition, many of the so-called psychotic developments of pregnancy do not manifest themselves until some time after delivery, so that the connection may not be recognized

Of all females who suffer from psychoses of various sorts, almost 9 per cent develop their mental disorders in connection with the reproductive experience. This places the problem squarely in the laps of obstetricians. There is no "psy-

chosis of pregnancy." But when one recalls the 9 per cent contribution of pregnancy to the total psychoses in females, and in the light of the fact that the incidence of psychoses among pregnant women is almost twice that among the female population generally, the author cannot but feel that pregnancy and its implications may provide distorting influences that are more intense than women are ordinarily called upon to face.

The types of psychoses which are associated with pregnancy are classified into 3 major divisions: Schizophrenic, manic-depressive and toxic-exhaustive. Of 891 cases in the author's survey, 35 per cent were toxic-exhaustive and 65 per cent functional. It is felt generally that the percentage of functional psychoses is likely to be higher among the prenatal cases than among those developing postnatally; whereas the toxic-exhaustive incidence climbs postpartum

The percentage incidence of psychoses associated with illegitimate pregnancies is greater than one finds in married cases

Concerning the outlook in the cases under discussion, it is generally agreed that the prognosis may be considered good in most instances, ranging from 76 per cent to 53 per cent recoveries

There exists in many quarters something akin to a superstition that psychoses occurring during pregnancy are likely to disappear with miraculous suddenness at the time the uterus empties itself. Except for an occasional toxic case, where the toxicity apparently is dependent specifically on the pregnant state, the regression of the mental abnormalities usually may be expected to be gradual

As to warning signals, the expectant mother's observable emotional reaction to childbearing and its various implications merits consideration. It is important to discover, if possible, how appre-

hensive she is regarding pain, and how courageous she usually is in the face of discomfort. The existence of a schizoid personality, and particularly the history of previous "nervous breakdowns" are warnings that should not be neglected. Unsuccessful attempts at abortion, in addition to the possible physical sequelae, frequently result in conscious and unconscious guilty feelings that may play havoc with the patient subsequently. The factor of illegitimacy may be disturbing.

In the majority of cases, properly interested management on the part of the obstetrician will eliminate the need for specialized psychiatric aid.

Pyelitis—The effect of *sulfanilamide* administered to 64 pregnant patients with pyelitis was studied by A. Barr.³⁵ Simple cases can be cured in from 4 to 5 days with sulfanilamide. Renal and toxic pyelitis requires a larger dosage of the drug and a longer time (14 days) to sterilize the urine. The treatment is more quickly effective than any other standard line of treatment for pyelitis in pregnancy, and now it should seldom be necessary to resort to ureteral drainage or termination of pregnancy in these cases. The immediate improvement in the general appearance of the patient and her obvious feeling of well-being shortly after the treatment is begun is in marked contrast to the depression of patients taking large quantities of alkalis. Catheterization of the ureters has been unnecessary in this series even in cases of the gross toxicity. Induction of premature labor was not necessary and all patients with the exception of the 2 in whom miscarriages occurred went to term.

In slight pyelitis, from 8 to 10 grains (0.5 to 0.6 Gm.) of sulfanilamide 3 times a day rapidly produced a remission of symptoms—usually within 48 hours. In the severe cases a dosage of from 28 to 38 grains (1.8 to 2.4 Gm.) a day was

required to sterilize the urine in an average of 14 days. In the toxic cases in which nausea and vomiting were prominent features, oral administration of the drug was impossible and daily injections of *prontosil* (Winthrop) were given in 2½ dram (10 cc.) doses, and in from 4 to 5 days administration of the drug by mouth usually was possible. Administration of *prontosil* did not seem so effective and in from 5 to 7 days, although there was a slow improvement in the general condition of the patients, there was no material change in the bacterial content of the urine. As soon as the administration of sulfanilamide by mouth was begun there was a rapid change in the general condition, and the urine was sterile in an average of 14 days as in the renal cases, with the same dosage.

Syphilis—The treatment of syphilis complicating pregnancy as observed at the Bellevue Hospital, New York City, is discussed by M. D. Speiser.³⁶ A study of the last 11,983 deliveries at Bellevue Hospital yielded 489 patients who were diagnosed as syphilitic, an incidence of 4.08 per cent.

The aim in the treatment is primarily to prevent the transmission of the disease to the offspring. The greatest reliance is to be placed upon the use of an arsenical, preferably *arsphenamine*; along with this a heavy metal, preferably *bismuth*, is used. Prior to the onset of treatment, a complete physical examination, blood pressure, and urinalysis must be done.

The routine employed varies with (a) The stage of the syphilitic infection, and (b) the period of gestation.

Treatment is interrupted in the presence of toxemia and other medical contraindications. Severe reactions likewise call for the prompt interruption of arsenical therapy.

Should the patient with early syphilis be seen for the first time during preg-

nancy, she is treated in much the same fashion as the nonpregnant early syphilitic patient. The treatment of the pregnant woman with latent syphilis varies with the length of gestation. Regardless of the length of gestation, however, treatment is always continuous and uninterrupted by rest periods. When therapy is started during the first trimester, it is well to begin with bismuth as a preliminary to the use of arsphenamine. Alternate series of 4 to 6 intramuscular injections of bismuth and 8 to 10 intravenous injections of arsphenamine are given and treatment is so arranged that the last month or six weeks is to be occupied with the administration of the arsenical. When treatment is started during the second trimester of pregnancy, the method used is continuous alternate therapy with slight overlapping of courses.

Before the first course of bismuth is completed arsphenamine is begun, and for the week or two of overlapping the patient appears at the clinic twice weekly. As in the previous group, the arsenical is employed during the last few weeks of pregnancy. In the final group, those who present themselves during the last trimester, continuous combined therapy is used. The arsenical is employed weekly until the end of pregnancy, thus perhaps allowing up to 14 or 15 doses. The bismuth is given on a separate clinic visit each week and may be interrupted for a few weeks following the series of 4 to 6 injections. The major difference between the treatment of the nonpregnant and the pregnant laden syphilitic woman is that in the latter the arsenical receives greater emphasis and the treatment must be continuous. When arsphenamine is employed, the initial dose is 0.1 Gm.; this is increased to 0.15 Gm. and subsequently to 0.2 Gm., at which level it is usually maintained throughout. Occa-

sionally in large women, the dose may be increased to 0.3 Gm. If neoarsphenamine is employed, the initial dose is 0.15 Gm.; this is increased to 0.2 Gm. and finally to 0.3 Gm. Occasionally they employed 0.45 Gm.

Urinalyses and blood pressure readings are done prior to each injection and the patient is questioned as to her subjective symptoms following the last dose of the arsenical. Last, the sclerae, mouth, wrists, and elbow bends should be carefully inspected for evidences of toxicity.

Intrauterine Fetal Death

Electrocardiography in Diagnosis—The presence of fetal heart sounds or fetal movements is often difficult to elicit especially during labor. Fetal electrocardiography is a new method for determining during pregnancy whether or not the fetus is alive. The technic and results of routine fetal electrocardiography during pregnancy are described by E. O. Strassman and R. D. Mussey.³⁷

The fetal electrocardiogram recorded in pregnancy and labor gives us records of documental value, tracings which show the action of the maternal heart and that of the fetus at the same time. The relationship between the circulation of the mother and that of the unborn infant can be studied under various conditions.

During the last 2 months of pregnancy, with the technic here described, about 87 per cent of fetal electrocardiograms were positive. That is, a negative result did not mean that the fetus was dead, but a positive result was definite proof that the fetus was alive.

The closer the approach to term, the higher was the percentage of positive fetal electrocardiograms, corresponding to the increasing size and increasing strength of the electric impulse of the fetal heart. In the last 3 weeks the per-

centage of positive fetal electrocardiograms ran up to 94 if the fetus was in vertex presentation. Among these cases the percentage of positives was higher than among breech presentations owing to the fact that in the presence of breech presentations the fetal deviations were deflected above the zero line and therefore were recognized with somewhat more difficulty (because of the confusing positive maternal waves) than were the fetal waves in the presence of vertex presentation which appeared deflected below the zero line. On the other hand, the diagnosis of breech or vertex presentation could be made without examining the patient, on account of the direction of the waves.

A fetal electrocardiogram was regarded as positive only if it was possible to follow the fetal waves all through the tracings and to give the exact fetal heart rate. The fetal waves occurred regularly, in a rhythm independent of that of the mother. The size of, and the distance between, the fetal deviations were constant. The fetal waves appeared first in that lead which was almost parallel to the axis of the fetal heart. The larger the fetus, that is, the later in the course of pregnancy, the larger was the number of leads which became positive and this made the diagnosis much easier. It was found justifiable to expect that 75 per cent of all electrocardiograms taken in the last 2 months of pregnancy would be positive in at least 2 leads and about 30 per cent in 4 leads. There was no use in taking electrocardiograms before the last third of pregnancy, since the fetal heart action was too weak to exert any visible influence on the tracings obtained by the technic adopted by the investigators.

Fetal electrocardiography is not to be considered as another pregnancy test but is meant to determine, during the last

period of pregnancy, especially during labor, whether the fetus is alive.

Placenta Previa

Diagnosis by X-ray—The diagnostic value of cystography in placenta previa is discussed by K. Jablonski and E. Meisels.³⁸ The method is of value especially for the cases in which the fetus is in the vertex position. Ude and Urner maintained that the distance between the lower outline of the fetal cranium and the contrast shadow of the bladder measures normally at the most 1 cm. and that this distance is taken up by the thickness of the wall of the urinary bladder, of the uterine wall and of the fetal scalp. Jablonski and Meisels, however, assert that the distance is dependent on the following factors: (a) The degree of dilatation of the lower uterine segment and the lifting of the bladder connected with this, and (b) the lowering of the fetal head. This explains why, between the seventh and tenth months of pregnancy, the distance becomes constantly smaller so that during the last weeks of pregnancy the outline of the head almost touches the shadow of the bladder. However, if a body is interposed between the fetal head and the uterine wall, such as for instance the placenta or a myoma, the distance is in excess of 1 cm.

The cystography is done in the following manner. After evacuation of the bladder by means of a catheter, 40 cc of contrast fluid (a 12.5 per cent solution of sodium iodide or another contrast substance) is introduced into the bladder. After withdrawal of the catheter, a ventrodorsal roentgenoscopy is made, with the patient in the reclining position and the central ray directed toward the rim of the symphysis.

The authors made this test on 30 pregnant women. In 16 of them hemorrhages had occurred during the second half of

pregnancy and the other 14 cases observed as controls. They found that this roentgenologic method permits the detection or exclusion of the placenta previa if it is of the central or lateral type. A placenta previa marginalis, particularly if located on the posterior uterine wall, usually cannot be determined by means of this method. Another disadvantage is that the method can be used only if the fetus is in the vertex position. However, the authors suggest that, in some cases of oblique, transverse or pelvic position, external version into the vertex position can be tried. They succeeded in accomplishing this in 3 cases.

PUERPERIUM

Lactation

Stimulation with Prolactin—The effect of prolactin on the secretion of milk is reported by J. R. Ross³⁹ The breast milk was pumped by an Abt electric breast pump and the amount obtained was measured carefully. Infants were selected who did not show signs of weight increase by the fifth day. Breast milk was then pumped from the mother and the total 24-hour secretion was measured for 1 or usually 2 days. Nine mothers received 2 intramuscular injections of 30 minims (2 cc.) of prolactin (80 Riddle units) and on the second day 2 intramuscular injections of 45 minims (3 cc.) and 12 patients were given a similar volume of prolactin containing 100 Riddle units per cc. A group of 10 patients acted as controls and received a similar amount of saline solution. The breast milk was pumped at intervals of 4 hours until the patient was discharged.

No untoward reactions were noted with the less concentrated prolactin. With the more concentrated prolactin,

however, reactions consisting of redness and induration varying in diameter from 2 to 15 cm. developed in 83 per cent of the cases. These cleared up in from 2 to 3 days. There was also a rise in temperature of from 100° to 102° F. (37.8° to 39° C.) in all but 1 case after the injections but it returned to normal in from 2 to 6 days. The higher concentration of prolactin administered increased slightly the secretion of breast milk during the remainder of the patient's stay in the hospital. Of much more significance, however, was the fact that 7 of 11 patients receiving this higher concentration of prolactin observed after discharge from the hospital nursed their infants completely, whereas of 8 such observed patients receiving the lower concentration of prolactin only 2 were able to nurse their infants completely. Of the 8 controls, only 1 nursed her infant completely.

Inhibition of Lactation—The inhibition of lactation with testosterone propionate in 21 patients were studied by R. Kurzrok and C. P. O'Connell⁴⁰ The total dose ranged from 50 to 150 mg. Two doses were given daily for 1 or more days and all injections were made deep in the gluteal region. The effect in only 2 instances was considered unsuccessful, 1 patient was completely relieved of symptoms on the fourth day and the other patient was injected with a total of 75 mg. of testosterone propionate divided into 3 doses. In the latter case the first injection was given on the first day postpartum. The symptoms of pain, fullness and engorgement of the breasts were not relieved. In view of the fact that lactation usually begins on the fourth day postpartum the inhibitory effect of testosterone propionate might have been exerted a little too early in this case. The results were excellent in the remaining 19 cases. It was not unusual

to find that, when doses of $\frac{2}{5}$ grain (25 mg.) were given, complete relief of all symptoms was obtained within a few hours after the second dose (8 hours after the first dose). In general, $\frac{1}{15}$ grain (4 mg.) or more of testosterone propionate was required to relieve all symptoms of engorgement of the breast. Complete relief of symptoms usually occurred within 48 hours. The best results were obtained from doses of $\frac{2}{5}$ grain (25 mg.) each. Once the symptoms were relieved there was no tendency for their recurrence after the injections were stopped.

Twenty-one cases of early lactation during the puerperium were treated with testosterone propionate, for the purpose of inhibiting lactation, by R. Kurzrok and C. P. O'Connell.⁴⁰ Usually the inhibition of lactation by the generally used therapeutic measures, and especially in their absence, is associated with pain, tenderness, engorgement and lumpiness of the breasts. Such breast symptoms require considerable nursing care and are very distressing to the patient. Testosterone propionate, in doses of $\frac{2}{5}$ grain (25 mg.), the authors claim, usually relieves such symptoms in about 24 hours without the addition of any other therapeutic measures. The hormone is injected twice a day, intramuscularly, in the buttocks. A total dose of $1\frac{3}{5}$ grains (100 mg.) may be given within 48 hours, although if complete relief occurs after the second or third dose no additional doses need be given. The puerperium was not otherwise affected by the hormone, and there were no unpleasant aftereffects.

Inhibition with Estrogen—J. Adrian⁴¹ used estrogen to the exclusion of all other therapeutic measures, in all cases in which an inhibiting treatment of the mammary secretion was justified, such as in cases of pulmonary tubercu-

losis, in cardiac defects of the mother, in stillbirths or in early death of the infant. In some cases 3 injections of 20,000 I. U. are required; in other cases a single injection of this quantity is sufficient. This treatment proved successful in 57 per cent of 100 cases. In the other 43 per cent the results were insufficient in that the secretion with expression of the breast persisted after the treatment. However, the result was nevertheless considerable in that the painful tension in the breasts, as well as the spontaneous secretion, ceased.

Breast Milk and Sulfanilamide Excretion—It is of considerable importance to know whether nursing mothers excrete sulfanilamide in their milk. H. Bauer and M. F. Gunderson⁴² reported the effect of sulfanilamide on streptococic mastitis in cows and stated that the amount of drug excreted in the cow's milk could be determined by a modification of Fuller's method for blood. J. S. Hepburn, N. F. Paxson and A. N. Rogers⁴³ found sulfanilamide in the milk of 16 puerperal women. The concentrations varied from 0.55 to 2.17 mg. per 100 cc. 24 hours after its initial administration.

F. L. Adair, H. C. Hesseltine and L. R. Hae⁴⁴ report an experimental study and found that sulfanilamide was excreted in the milk as in the urine, partly unchanged and partly as the conjugated acetyl form. This may be of some importance since it has been shown that in animals the toxicity of acetyl sulfanilamide is somewhat greater than that of the free sulfanilamide.

With doses of 30 and 60 grains (2 and 4 Gm.) the total amount excreted was never greater than 1.5 per cent of the amount of the drug administered. It was still being excreted in small amounts 72 hours after medication had been discontinued.

Sulfanilamide is transmitted to the placenta and fetus of the rabbit and is associated with a marked increase in the mortality of the young. Sulfanilamide, according to Adair, *et al.*, should be administered only with the utmost caution during pregnancy and the period of lactation. If administered to the mother, breast feeding should be discontinued during the period that sulfanilamide is excreted in the milk.

H. L. Stewart, Jr., and J. P. Pratt⁴⁵ found that free sulfanilamide is excreted in human breast milk in concentrations closely corresponding to the values present in the blood stream. When oral administration of sulfanilamide is discontinued, the concentration in the milk rapidly falls. Breast-fed babies of full-time nursing mothers did not show clinical evidences of toxic manifestations when sulfanilamide was present in breast milk in concentrations of 7 mg. per 100 cc. Traces of the drug were present in the blood of the baby. The urine of these babies contained amounts varying from 1 to 26 mg per 100 cc. during a 24-hour period.

A nursing baby cannot obtain an adequate therapeutic dose through the milk of a mother receiving an average clinical dose. Sulfanilamide was present in the cord blood and amniotic fluid of 6 women following the oral administration of 5 grams (0.3 Gm) of the drug every 4 hours throughout labor.

Puerperal Infection

Treatment—The treatment of this condition is discussed by P. Trillat and R. Burthiault⁴⁶. They report 4 cases of puerperal infection, in 3 of which the blood cultures were positive, in 1 case for the streptococcus, in another for the enterococcus, and in the third case for the staphylococcus albus and the bacillus subtilis (2 cultures). All of these cases

were of a severe type and the patients had failed to improve with the usual methods of treatment; they were finally treated by the continuous intravenous injection of an alcoholized glucose solution. Two of the patients recovered, and 2 died. In 1, death was found to be due to an acute diffuse pulmonary tuberculosis, a latent tuberculosis having apparently been activated by the postpartum infection and by the treatment; the blood culture in this case was negative. In the other fatal case, some improvement was noted when the treatment was instituted, but it was apparently too late.

The solution employed consisted of $\frac{2}{3}$ ounce (20 cc.) of *ethyl alcohol* (95 per cent) and $1\frac{2}{3}$ ounces (50 Gm) of *glucose*, and water to make 1 quart (1000 cc.). It was put up in containers holding 1 pound (500 Gm.). The apparatus was adjusted to inject 2 quarts (2 liters) of the solution in 24 hours, about 30 drops per minute. As a rule the injection was continued for 4 days. When the treatment was first instituted the patient usually had a chill, but no further chills occurred; patients who responded well to the treatment noted a feeling of well-being after the first few hours.

This form of treatment is recommended especially in cases with repeated chills, which indicate a spread of the infection and invasion of the blood stream, even if no chills occur, the treatment is also indicated if the blood culture is positive. In the authors' patients who recovered, the treatment was not instituted until the fifth or sixth day after repeated chills had occurred daily.

The treatment of puerperal sepsis by *prontosil* and allied compounds is reported by D. B. Brown.⁴⁷ The author uses *prontosil* (Winthrop) in the treatment of 39 cases of puerperal sepsis due to the hemolytic streptococcus (Group

A of Lancefield) and in the treatment of 35 cases of mastitis and 8 cases of *Bacillus coli* infection of the urinary tract. Of the 39 patients suffering from puerperal sepsis there were 27 with local infection of the uterus, 8 with septicemia (2 of whom also had general peritonitis) and 4 cases of general peritonitis alone. Prontosil was administered intramuscularly and by mouth. Prontosil soluble was used in all the cases of puerperal sepsis, but in 4 mild cases the dosage was not more than 15 grains (1 Gm.). In the first 5 cases treated the first dose was given intravenously but in the remainder of the cases by intramuscular injection. It was given in the dosage of 20 cc (0.5 Gm.) 2 or 3 times daily, the amount being decreased as the patient improved.

There was marked improvement in 11 of the 27 patients with local infection of the uterus after the administration of prontosil; in 1 patient it had no effect and in 1 death occurred from agranulocytosis after the sepsis had apparently been controlled. These patients were seriously ill. In the 11 successfully treated cases the average total dosage of prontosil was 1 ounce, 3 drams (42.6 Gm.). The 14 other cases were of mild or moderate severity and recovery would almost certainly have occurred without prontosil. Of the 8 patients with proved septicemia 6 recovered—a mortality of 25 per cent. One of these patients who died was the first to be treated with prontosil and the dosage was inadequate. The second fatal case was admitted 4 days after a manual removal of the placenta. Of the 4 patients with general peritonitis not associated with a septicemia, all recovered. Relapses occurred in 3 of the patients but responded when the drug was readministered.

The 35 patients with mastitis have been treated by the administration of

sulfanilamide, *benzyl aminobenzene sulfonamide* or *sulfonamide-P (sulfanilamide)* in the dosage of from 30 to 45 grains (2 to 3 Gm.) daily. The average duration of treatment was 5 days. All were severe cases and a few of the patients in whom mastitis developed in the hospital have not had any abscesses of the breast, that is, since prontosil was used for acute mastitis. The author has also used sulfanilamide in the treatment of a number of patients admitted for abscesses of the breast and although most of these have required incision they have all appeared to heal more rapidly than usual.

Calcium Therapy—The value of *calcium therapy* in puerperal infection is discussed by W. J. Cusick.⁴⁸ The author treated 26 patients with puerperal infections without a demonstrable cause outside of the pelvis in whom the temperature persisted above 101° F (38.3° C) for more than 48 hours. The chief complaint was abdominal pain and tenderness, located in the lower part of the abdomen. Other complaints were frequency and urgency of urination. In 14 cases the vaginal discharge was putrid. Microscopic examination of the discharge from both the cervix and the urethra was positive for gonococci in 2 cases and negative in 24.

The treatment employed included *rest in bed*, an *ice bag* to the lower part of the abdomen, *elevation of the head of the bed*, *fluids in quantity*, *magnesia magma* when necessary and no sedatives, douches or powerful cathartics. One ampoule of 10 cc of the 10 per cent product of the *double salt of calcium gluconate* and *calcium galactogluconate* was injected intragluteally and intravenously each day, after the needle of a 20 cc syringe was inserted into a vein and 10 cc. of blood was withdrawn and permitted to mix with the

calcium solution. Calcium gluconate, 1 heaping teaspoonful 3 times a day before meals, was given in warm milk. With this treatment the average hospitalization period was 14 days, varying from a minimum of 9 to a maximum of 22 days. The pain disappeared in 19 patients within 34 hours, in 4 in 48 hours and in 3 within 72 hours. Rigidity of the abdomen disappeared within 6 days. The temperature curve returned to normal within an average of 6 days. At the time of dismissal the pelvis of all patients were examined and if there was any evidence of an inflammatory process, calcium gluconate was continued orally 3 times a day.

Prophylactic Treatment with Sulfanilamide Compound—S. N. Hayes and A. Sami⁴⁹ report the results of the administration of p-benzyl-aminobenzene sulfonamide (proseptasine) prophylactically in all emergency cases of puerperal infection admitted to the hospital. From January to June, 1937, they gave 2 tablets 3 times daily (3 Gm.) for 4 days. From July to December, 1937, they gave 4 tablets 3 times daily (1½ drams or 6 Gm.) for 4 days. There was a reduction of morbidity due to genital sepsis from 22.16 per cent (1934) and 16.94 per cent (1936) to 11.45 per cent in 1937, during which time the drug was given prophylactically. This reduction occurred chiefly in the abnormal cases; the membranes were ruptured and infection was potential or apparent, the patient had been in labor from a few hours to a few days, obstetric shock was usually present, multiple vaginal examinations or attempts at delivery had been practiced or the case was usually terminated by means of an obstetric operation. No ill effects have been observed as a result of the administration of the drug; as much as 4 ounces (125 Gm.) has been administered without signs of

toxic symptoms. The authors suggest that larger doses of the drug be used. Although a reduction of 5 per cent in morbidity is not striking, they feel that it is encouraging enough to advocate further investigation with increased dosage.

Concentrated Streptococcus (Hemolytic) Antitoxic Serum—The demonstration in 1925 of the production of toxin by hemolytic streptococci from patients with puerperal sepsis and the subsequent production of an antitoxin introduced a new and rational basis for serum therapy for puerperal sepsis. Subsequent clinical studies of the effect of the *antitoxic serum* on puerperal sepsis indicated its therapeutic value in the early stages. The present study, begun in 1928, was undertaken by A. F. Lash⁵⁰ to check the value of serum therapy in a series of patients with puerperal sepsis in which alternate patients were treated with serum.

The amount of serum used depended on the clinical response. Of the 40 patients, 12 received 40 cc., 9 received 60 cc., 6 received 80 cc., 6 received 100 cc., 5 received 120 cc. and 1 received 160 cc. No immediate reaction followed the use of the concentrated serum. Although the intravenous injection gave a quicker therapeutic response, the intramuscular route was most often chosen for the sake of safety. The difference in rate of absorption between the two may not be great, but the effect is much more striking with intravenous administration. Late serum sickness, that is, erythema, urticaria and swollen and tender joints, occurred from 6 to 9 days after the administration of the serum in 40 per cent of the patients, which is a high incidence. No serious consequence followed the serum sickness, except in 2 patients: 1 had persistent sciatica and the other had toxic encephalitis (no or-

ganisms on smear or culture). They recovered and the relation to serum therapy was dubious.

An analysis of the deaths in the treated group shows that the cause of death was generalized peritonitis. The negative value of the serum in this group was not due to the delay in the administration of the serum except in probably 1 instance but rather due to the rapidity of the extension of the infection (generalized peritonitis). It is again evident that serum is of no value in the treatment of this type of infection.

The author concludes that the value of antitoxic serum therapy in the treatment of early hemolytic streptococcus puerperal sepsis is demonstrated by the marked reduction in mortality and residual pathologic changes in a controlled series of cases.

The early diagnosis of hemolytic streptococcus puerperal sepsis is essential for the successful use of the antitoxic (hemolytic) streptococcus serum.

Failures despite early therapy may be due to the abnormally rapid progression of the infection (fulminant form of generalized peritonitis).

TOXEMIAS OF PREGNANCY

The nature of the toxemias of pregnancy are discussed by J. P. Peters.⁵¹

One of the first facts that attracted attention was the frequency with which pyelitis appeared as a precursor, associate or sequel of toxemias. Of 320 patients whose records were sufficiently complete to permit analysis, 41, or 13 per cent, suffered at one time or another from conditions generally included under the terms pyelitis and pyelonephritis. Of 23 patients examined postmortem who died either from acute toxemia or from remote results of conditions that seemed to originate with toxemias, 10 had pyelitis or pyelonephritis.

Of 43 patients with eclampsia with adequate histories, 18 had definite records of antecedent renal or vascular disease, chiefly pyelitis, nephritis, essential hypertension and previous attacks of toxemia. Apparently the major features which predispose to eclampsia are diseases of the kidneys or arteries. Of 44 who have been traced, 33 have died of or are known to have chronic renal or arterial disease, evidence that eclampsia insults chiefly kidneys and blood vessels.

Little has been found to support the general impression that toxemias are manifestations of some abnormality of metabolism or of any derangement or discoordination of endocrine function. Certain anatomic and functional departures from the nonpregnant norm may heighten the susceptibility of the pregnant woman to renal and vascular insults. First among these conditions would seem to be ureteral obstruction, which, by impeding the free discharge of urine, enhances the risk of infection, reduces the capacity to eliminate an infection which has already become established and affects the course of nephritis unfavorably, often disastrously. Reduction of the concentrations of albumin, bicarbonate and sodium in the blood serum and increase in the lipoids, changes that are not in themselves sufficiently marked to give rise to any serious symptoms, are similar to the changes observed in certain types of renal disease and therefore may heighten the susceptibility of the pregnant woman to the effects of circulatory or renal disturbances. Other conditions, such as acidosis, lactic acidemia, ketonemia, hyperglycemia and hypoglycemia, seem to be results, rather than causes, of toxemic disorders.

Pregnancy undoubtedly contributes a peculiar coloration to these renal or vascular disorders, causing relatively benign diseases to burst into a malignant state

and causing the frequency of renal and vascular disease in pregnant women to exceed that in nonpregnant women of comparable ages.

The histologic changes in the glomeruli and tubules of a large proportion of patients who die in the acute stages of toxemia, with or without eclampsia, have certain features which are different from the lesions commonly found in acute nephritis. This may indicate that the pregnant woman reacts according to a distinctive pattern to vascular and renal insults.

So far as ultimate treatment of the problem of toxemias as a whole is concerned, the implications of this study must be obvious. Patients with antecedent renal or vascular diseases cannot safely be carried through pregnancy. Women who have pyelitis when pregnant seldom escape irreparable and enduring damage if the pregnancy is allowed to proceed. Treatment seems to be of little benefit, since infections of the urinary tract cannot be eradicated in the presence of obstruction of the ureters. Toxemias of all kinds leave behind them marks, usually in the vascular system, that cannot be eradicated. Even if they do not manifest themselves immediately in progressive arterial or renal disease, they almost invariably flare up in subsequent pregnancies, to cause further damage. There are no clinical distinctions between toxemias in this respect. The only rational treatment, therefore, is the prevention of pregnancy in women with disease of the arteries and kidneys, and in those who have had previous attacks of toxemia, and the immediate termination of pregnancy on the appearance of the first signs or symptoms of hypertension or renal disease familiarly ascribed to toxemias.

Early Toxemia—Treatment of Vomiting—J. M. McGowan, J. O.

Baker, A. M. Torrie and J. Lees⁵² discuss a new treatment for hyperemesis gravidarum.

Because of the close relationship between pregnancy and the origin of biliary disease and because spasm of the second portion of the duodenum produced by morphine was accompanied in some cases by nausea or biliary colic, it was decided to study the duodenum in patients suffering from the vomiting of pregnancy.

Roentgenologic studies were made of the duodenum in 2 women suffering from the vomiting of pregnancy. A spasm of the second portion of the duodenum was noted in each case. This was readily relaxed by inhalation of *amyl nitrite*. *Glyceryl trinitrate*, $\frac{1}{100}$ grain (0.65 mg.), under the tongue 3 times a day before or after meals has been used for the control of vomiting in 12 cases, with consistently good results.

The vomiting of pregnancy sometimes is associated with a spasm of the second portion of the duodenum with probably a decrease in tone of the pylorus and stomach. Inhalation of *amyl nitrite* relaxes the duodenal spasm, produces proper emptying of the duodenum into the jejunum and restores gastric and pyloric tone.

Hyperemesis Gravidarum—Various remedies have been advocated during the last few years and all have helped some patients, if not by their physiologic activity, then by their psychic effects. *Iodine* in the form of the compound solution is of benefit in many cases. *Insulin* has helped in some cases but this substance must be used with great caution and preferably in combination with dextrose. *Adrenal cortex extract* has been used in many cases and some reports are enthusiastic about the results.⁵³ The same enthusiasm has been expressed for the use of *cevitamic acid*.⁵⁴ Likewise benefit is claimed for the use of *para-*

thyroid extract with calcium.⁵⁵ Some patients have been benefited by having their own urine instilled into the rectum.⁵⁶

Recently it was found by J. H. McGowan, J. O. Baker, A. M. Torrie and J. Lees⁵² that the vomiting of pregnancy sometimes is associated with a spasm of the second portion of the duodenum with probably a decrease in tone of the pylorus and stomach. These authors found that *glyceryl trinitrate* satisfactorily controls a certain number of cases of vomiting of pregnancy.

Nausea and Vomiting—J. W. Finch⁵⁷ reports on work done to prove that nausea and vomiting accompanying pregnancy are due to an allergic reaction of the patient to the secretion of her own corpus luteum graviditatis.

Patients were tested by cleansing the skin with alcohol and injecting intradermally from 0.02 to 0.03 cc of progestin in sterile cottonseed oil and recording reactions 15 and 30 minutes later. Reactions were calibrated from negative to ++, according to the size of the wheal and the surrounding erythema produced just as in intradermal injections of any food, drug or pollen extract or animal dander to determine a patient's degree of sensitivity. A control injection was made with sterile cottonseed oil in the same arm. The majority of the tests were made on the volar aspect of the forearm. A few patients were tested with a solution of progestin in sterile almond oil but the cutaneous reactions to the almond oil were so much greater than those to the cottonseed oil that the latter product was used in the remainder of the cases. One interesting notation has been that several of the pregnant patients who were nauseated and gave 3+ or 4+ reactions to the progestin intradermally have complained as late as 5 or 6 weeks after the intradermal injection that when they become nause-

ated severely the area of injection again becomes irritated and forms a wheal with a surrounding erythema and an itching sensation.

If further investigation confirms these observations, one might well assume that a patient desiring pregnancy could be tested for sensitivity to progestin and, if found sensitive, could be desensitized before impregnation or before the corpus luteum of pregnancy reaches the stage of enlargement necessary to produce the symptoms of nausea and vomiting. This treatment would consist of graduated doses of progestin injected at closely spaced intervals until the patient is desensitized and the symptoms either do not develop or are relieved if they are already developed.

Value of Urea Clearance Test—The results of 671 urea clearance tests performed on 243 pregnant women is discussed by D. B. Brown.⁵⁸

The urea clearance test was first determined for normal pregnant women and then tests were made both before and after delivery on women with toxemia and on some patients who had pyelitis of pregnancy. A normal clearance test does not necessarily mean a normal kidney, as the test may be normal until from two-thirds to three-fourths of the renal tissue has been rendered functionless and also the clearance value is influenced by an alteration in the circulation rate and the supply of oxygen to the kidneys so that the results are lowered by severe anemia and cardiac decompensation. A low clearance value in an apparently well patient should be repeated and it must always be kept in mind that variations of less than 20 per cent are of no significance.

The clearance results in the present series were less constant after than before delivery. In severe renal damage, the clearance is more fixed than in normal persons. Each patient, therefore, must be

considered separately. The urea clearance test extends but never replaces clinical investigation. The differential diagnosis between pre-eclamptic toxemia, chronic nephritis and essential hypertension is made much easier by the urea clearance test. Before delivery a high value excludes chronic nephritis and if the blood pressure remains high with little other evidence of toxemia and a high clearance the case is probably one of essential hypertension. If the clearance is low the result is of no value in pregnancy in the differentiation of pre-eclamptic toxemia, chronic nephritis and essential hypertension but the result after delivery is of great value—most patients suffering from pre-eclamptic toxemia show a rapid rise within a week or two of delivery, while in chronic nephritis the percentage rise is much less and the clearance never reaches a normal level.

The follow-up of patients shows that if the clearance is high during the toxemia, the prognosis is good even if the degree of toxemia is clinically severe, and the same may be said if the clearance rises to more than 100 per cent within a week or so of delivery even if the clinical condition lags behind. The clearance test is of most value several months after delivery when low tests show definite renal damage at a time when clinical signs may be slight or absent, although possibly on repeated clinical examination some evidence may be found in practically all cases.

A low urea clearance is sufficient in the author's opinion to forbid a future pregnancy for at least 2 years, when further clinical examination and the clearance test should be repeated. A urea clearance below 80 per cent is strongly suggestive of renal damage; therefore a further pregnancy is not wise. The clearance test is also useful during the treatment of toxemia; if the test is

rising or remaining stationary, conservative treatment can be continued.

Treatment—A treatment based on a new concept of the etiology of the toxemias of pregnancy is presented by F. L. McPhail.⁵⁹ The author maintains that urinary solids should never be allowed to be retained on account of the accumulation of urinary waste and electrolyte in the blood plasma, as a result of impaired renal function. An attempt to secure a neutral ash is important, for if renal function is hampered a disturbance in water balance may occur with a resulting toxemia. The mechanism by which water is displaced or added to in a toxic individual and the reaction of the tissues and cells to such a toxemia are outlined. The effect on the kidney shows the most striking abnormalities in toxemia; it is believed that toxemia will not develop when no impairment of renal function exists. **Dehydration** is important and the proper use of the **tonic solutions of dextrose** has been invaluable in lessening the maternal and fetal mortality in the toxemia of pregnancy.

The treatment of *mild toxemia* is simple; its progress also is simple and may be averted. The success of treatment depends on the co-operation of the patient. **Fluids are forced.** A urinary output of 2500 cc. will be ample unless great renal impairment exists. A **neutral diet** is prescribed. As sodium is a predisposing cause of edema, **foods with a low sodium content** are chosen, and for the same reason sodium chloride and sodium bicarbonate are eliminated.

Severe nonconvulsive toxemia is treated in a similar manner. The patient should be observed more closely, because of the severity of the symptoms. Hospital care is of great value. The patient with severe pre-eclampsia may be treated over a long time if large quantities of fluids are given and if the urinary out-

put is correspondingly large. A *neutral diet* is necessary, as it does not disturb acid base equilibrium.

In the case of the *convulsive toxemias*, fluids cannot be given by mouth; therefore a parenteral route must be chosen. Fluids are more rapidly absorbed when given intravenously, but the subcutaneous method of administration is also valuable. The object is to give *large amounts of fluid*. Hypertonic dextrose solution dehydrates the cells. Isotonic dextrose solution makes water available to the cells. Therefore as the cells are already dehydrated and as hypertonic dextrose solution will increase that dehydration, *isotonic dextrose solution* is given.

A convulsive patient weighing 150 pounds (68 kg.) should have the following needs considered in the first 24 hours: Water to hydrate the cells, 4100 cc.; urinary water, 3000 cc.; vapor water (skin and lungs), 1000 cc.; total, 8100 cc. A large estimate must be made for urinary water if the kidneys are to excrete large amounts of retained urinary solids.

Very little medication is necessary even though convulsions are present. Usually an initial intramuscular injection of *soluble phenobarbital* will control the convulsions until intravenous treatment is instituted. It has not been necessary to repeat this medication, as the irritability disappears as fluids are given.

Two thousand cubic centimeters of 5 per cent dextrose solution may be given intravenously in about 2 hours. After 1000 cc. have been given, the administration of 5 per cent dextrose solution by hypodermoclysis is started. A total of 4000 cc. of the solution is given in about 8 hours. The fluid given subcutaneously is absorbed very rapidly. Diuresis is not expected immediately as available water

will first replace that lost by the dehydrated cells. Within 12 hours it is unusual if a patient will not drink water when encouraged. Water is given freely by mouth, but only water. It usually is necessary to give fluids by the parenteral route for several days before a patient will take enough by mouth.

It is generally true that a patient treated in this manner will regain consciousness before renal excretion is re-established. Convulsive patients are not given food until after 3 days of freedom from convulsions. They are then treated as patients with severe nonconvulsive toxemia.

Vitamins—A new approach to the problem of the cause of pre-eclampsia and eclampsia is presented by A. C. Siddall.⁶⁰ This is based on the suggestion that:

1. The normal function of the pituitary body is possible only when an adequate supply of vitamin B₁ is available and vitamin B₁ may be necessary for the pituitary as iodine is for the thyroid gland.

In the nonpregnant female, a deficiency of vitamin B₁ leads to beriberi, the symptoms of which are produced by hypofunction of the pituitary body. The symptoms of beriberi include disturbed carbohydrate metabolism, edema, low blood pressure, atrophy of the varies and atony of the gastrointestinal tract.

In the pregnant female, this deficiency of vitamin B₁ results in overcompensation or malignant hyperfunction of the pituitary body, thus producing the symptoms of toxemia, for example, disturbed carbohydrate metabolism, edema, elevated blood pressure, nausea and vomiting, increase in prolan, and decrease in estrin in the blood.

An adequate and constant supply of vitamin B₁ should prevent toxemia and perhaps cure it. This new concept har-

monizes for the first time practically all of the conflicting findings and confusing manifestations of toxemia. This is preliminary report and is being further investigated

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ORTHOPEDICS

By JOHN R. MOORE, M.D., and JESSE T. NICHOLSON, M.D.

BACK PAIN

Diagnosis and Treatment of Sacroiliac Conditions by the Injection of Procaine (Novocain) — K O Halde-
man and R. Soto-Hall¹ described a

procaine was injected by means of a spinal puncture needle. The needle was directed toward the involved joint at a 45-degree angle on the level with the first sacral spinous process at a point

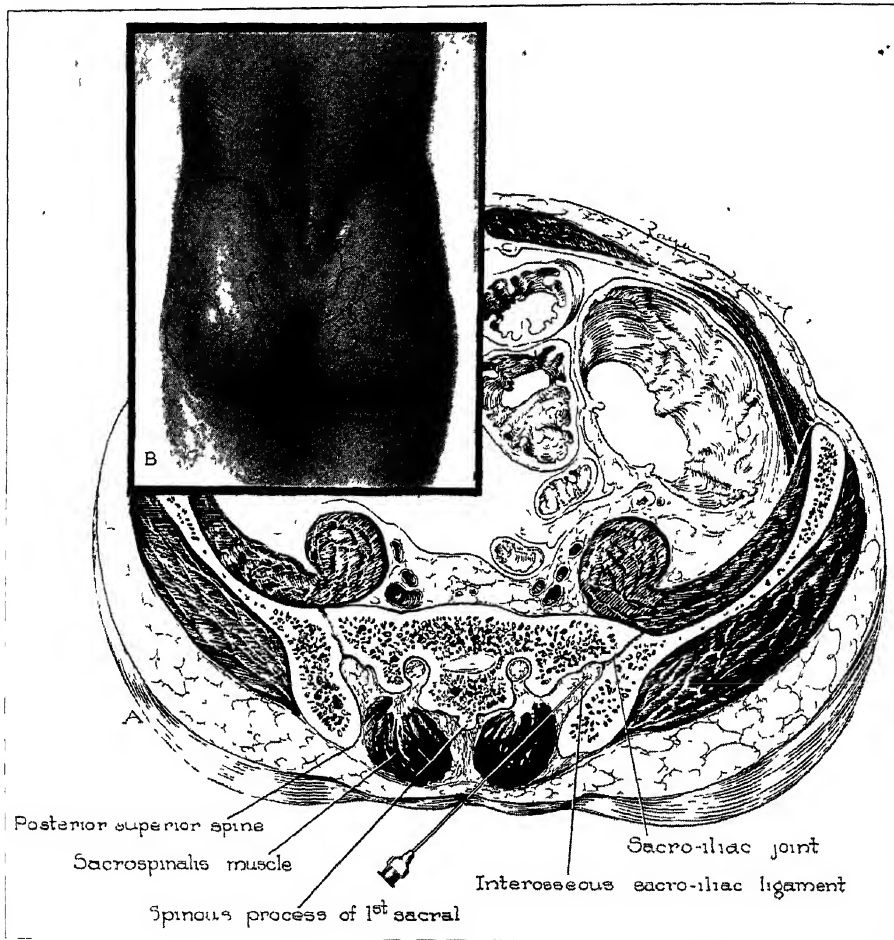


Fig 1

(Halde-
man and Soto-Hall J Bone and Joint Surgery (July) 1938)

method of *injection and manipulation of the sacroiliac joint* which gave relief in 60 per cent of the 42 cases of probable chronic sacroiliac strain. The patient was placed prone on the table after the oral administration of 3 grains of sodium amytal. Twenty to 30 cc. of 1 per cent

midway between the posterior superior spines of the ilia (see Fig. 1) The procaine was injected slowly while the needle was being inserted. When bony resistance was encountered the needle was partially withdrawn several times and reinserted so as to spread the novocain

along the joint. After 10 minutes the manipulations were started. These included straight leg raising, hyperextension of hips with knees flexed and rotation of shoulder to opposite side with pelvis fixed. The back was strapped with adhesive and the patient permitted to leave. In a few cases an exacerbation of sciatic pain occurred a day or two later and an analgesic was required. When relief was transitory, a repetition of procaine injection after a week usually resulted in further improvement.

In 3 patients in whom symptoms recurred after a few hours following the procaine injection in the sacroiliac region, lipiodol studies revealed a deformity of the spinal canal. The explanation was the possibility of postural strain of the sacroiliacs resulting from muscle spasm.

Lesions of the Intervertebral Disc and Ligamenta Flava

H. C. Naffziger, V. Inman, and J. B. Saunders² described the ligamenta flava as predominantly yellow elastic tissue adjoining the adjacent laminae and articular processes of the spine. The medial half was the broader and thicker part which tapered off as it extended laterally. This structure was attached predominantly to the articular processes and was related to the capsule of the articular facets. The interlaminar portion was attached to the outer border of the inferior lamina, the anterior margin of which sometimes exhibited sharp thin plaques or spicules of bone which extended up into the ligamentum flavum. These spicules had been regarded as ossification of the ligament but were more likely the ossific extension from the bone attachment. The attachment on the lower border of the superior lamina also was indicated by a ridge but the spicule formation had not been observed. A

description was given of the folds of lateral extension of ligament about intervertebral foramen and the relationship of this fold to the intervertebral discs lying anteriorly. A hypertrophy of the ligamentum flavum thereby created a pressure on the spinal nerve as it emerged from the dural sac. Protrusion of the intervertebral discs from ruptured nucleus pulposus could readily involve the nerve passing to the foramen.

The findings were based upon autopsy observations. The hypertrophy was explained by a tearing of the ligamenta flava and mechanism causing lateral bending and forward flexion of the spine. When torn, the fibers were retracted and healing occurred by scar formation which underwent hypertrophy. These changes in the ligamenta flava had been entirely limited to the lumbar region in the authors' experience, whereas the protrusion of intervertebral discs occurred at any level in the spine. The diagnosis could usually be made upon sciatic pain which is aggravated by straining, coughing and sneezing. Listing of the spine was common. This was not necessarily to side of the lesion. Absence or altered achilles reflex was frequent, in motor or sensory changes dependent upon the localization and structures compressed. These were more common on the outer side of the calf and areas supplied by the popliteal nerve. Sensory loss was never pronounced. Atrophy of the peroneal muscles was common in longstanding cases. Spine x-rays were not diagnostic, although in some there was a narrowing of the intervertebral discs at the affected area. Spinal puncture with the induction of lipiodol at as low a level as possible was the means of establishing the diagnosis. Occasionally the dural canal was encroached upon enough to give a positive Queckenstedt's test. The differential

diagnosis between extrusion from the intervertebral disc and thickening of the ligamentum flavum was not readily made but the operative approach was the same for both.

Pathologic Conditions of the Spine

L. A. Hadley⁸ wrote about the x-ray diagnosis of disturbance of the interverte-

lesions showed an encroachment of the nerve by masses of connective tissue over the posterior joint capsule and disc margin. The symptoms of such a muscle lesion were those of radiculitis with pain corresponding in distribution to the involved nerve root, either brachial, intercostal, abdominal or sciatic. Occasionally, there was disturbance of reflexes,

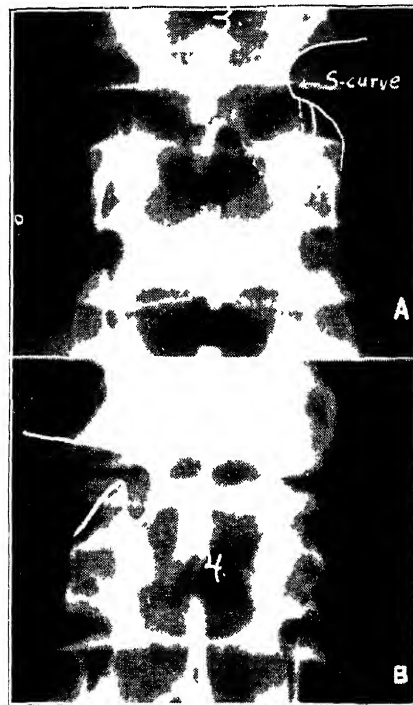


Fig. 2. *A*—Normal S curve and posterior articulations between third and fourth bodies. *B*—Subluxation of the posterior articulations, with a break in the S curve at both third-fourth and fourth-fifth levels. (J. A. M. A. (Jan. 22) 1938.)

bral foramina. These were found in segments which had lost the intervertebral discs. Due to the thinning of the discs the posterior articulations overrode, producing a luxation. On the x-ray film this could characteristically be shown by the loss of the "S" curve. The "S" curve was formed by the shadow produced by the normal articulation of the inferior and the superior articular facets. When the facets were luxated, they overrode and the "S" curve was distorted. The pathological sections of such

muscle atrophy or Dejerme's sign (pain of nerve root distribution on coughing, sneezing or bearing down). The pain was not along the course of the nerve but could be produced by pressure over the nerve roots. The treatment of this condition was not discussed.

BACKACHE

Manipulative Treatment Without Anesthesia—F. A. Jostes⁴ advocated manipulation of backs without anesthesia.

Contraindications to manipulation were subjects with cardiac decompensation and cases of chronic low back pain who had not been carefully studied for such conditions as fracture, dislocation, neoplasm, tuberculosis, arthritis, osteoporosis and osteitis fibrosa cystica. The subject with-

knees, keeping spine arch in flexion. The hands were brought toward the knees and the foot of the side opposite that of pain was advanced. The hands were placed on the flexed knee and the subject lifted himself by pushing down on knee. The subject got into a bed which



Fig 3—The pad for manipulation has a non-skid rubber base and a smooth leather cover, on top of which is placed a thin cotton pad plus a pillow (F A Jostes J Bone and Joint Surg (Oct) 1938)

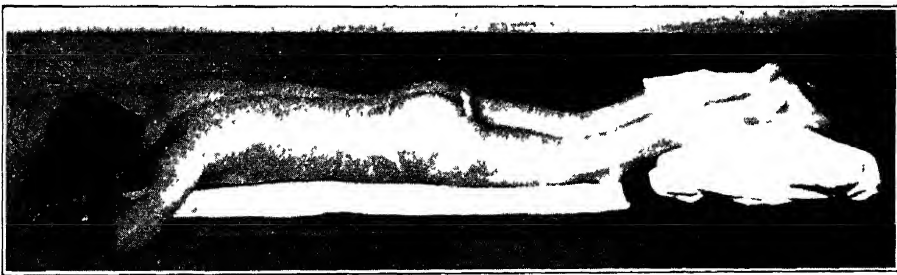


Fig 4—The patient lies prone with the hamstrings relaxed, due to the fact that the legs and feet are slightly elevated over a pillow. Complete relaxation is essential to effective manipulation (F A Jostes J Bone and Joint Surg (Oct) 1938.)

out clothes laid prone on the floor which was covered with a sponge rubber mat. After massaging the gluteal and lumbar muscles to obtain relaxation, the manipulations were carried out in a routine.

Following the manipulation the subject was taught to rise from the prone position by first getting on hands and

had boards under a hair or felt mattress in the center of which pillows had been arranged to maintain spinal flexion with the patient prone. Infrared heat at a distance of 30 inches was applied for 30 minutes every 4 hours. The subject practiced alternate straight leg raising twice daily. The subject could not use the usual

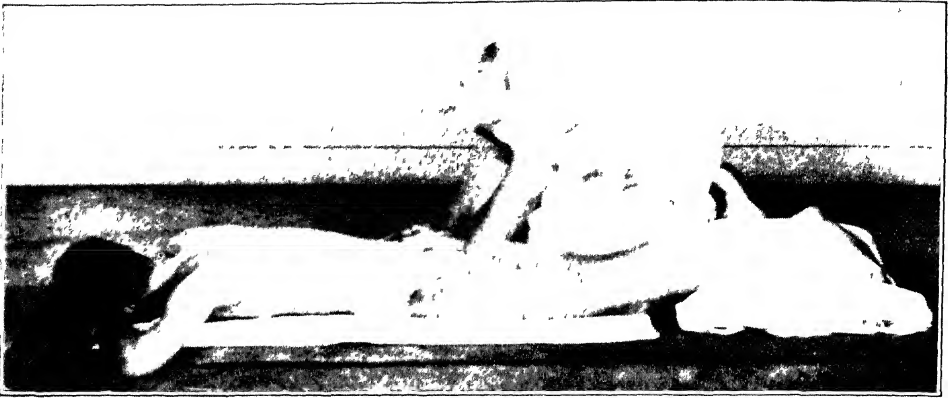


Fig. 2. Demonstrating the deep kneading massage of the gluteal muscles (E. A. Jostes—J. Bone and Joint Surg. (Oct.) 1938.)



Fig. 3. Showing extent of massage over sacrospinalis muscles up to and including the shoulder girdle (E. A. Jostes—J. Bone and Joint Surg. (Oct.) 1938.)



Fig. 7—Showing the position for Maneuver 1 of the actual manipulation. The thumb is thrust forward and downward, the shoulder is rotated backward (Flexes left sacroiliac joint and stretches posterior sacroiliac ligament. Some rotary movement to lumbosacral joint.) (F. A. Jostes—J. Bone and Joint Surg. (Oct.) 1938.)



Fig. 8—Maneuver 2—reverse of Maneuver 1. (Extends left sacroiliac joint and stretches anterior sacroiliac ligament, also rotates lumbosacral joint in opposite direction to Maneuver 1.) (F. A. Jostes—J. Bone and Joint Surg. (Oct.) 1938.)

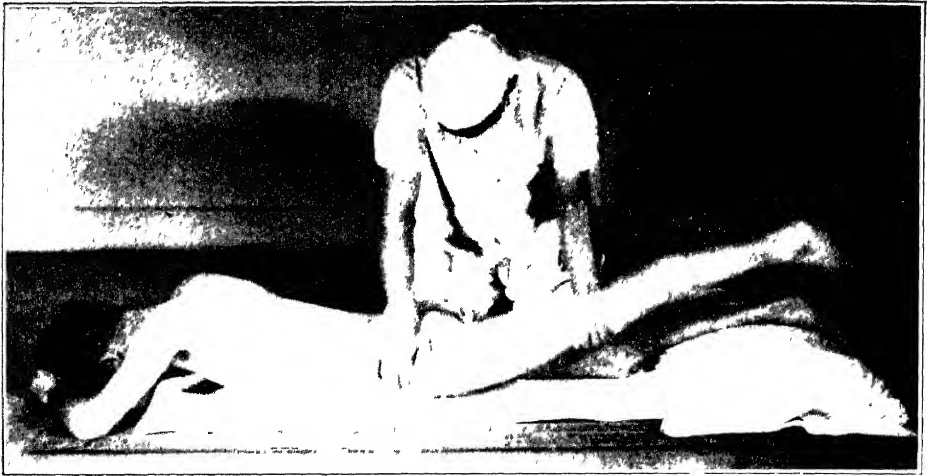
*A**B*

Fig. 9.—Maneuvers 5 and 6—hyperextension of thighs—first with the fulcrum on the ilium, second, with the fulcrum on the sacrum. In many cases the fulcrum on the sacrum creates much more pain than when it is on the ilium. (Primarily stretches iliofemoral bands—secondarily rotates sacroiliac joints clockwise on sacrum.) (Cf. A. Jostes—J. Bone and Joint Surg. (Oct.) 1938.)



B

Fig. 10—Maneuver 7—passive flexion of spine at lumbosacral level plus rotation of pelvis with spine in acute flexion. (Flexion and rotation of lumbosacral joint—stretching of sacrospinous muscles.) (P. A. Jostes—J. Bone and Joint Surg. (Oct.) 1938.)

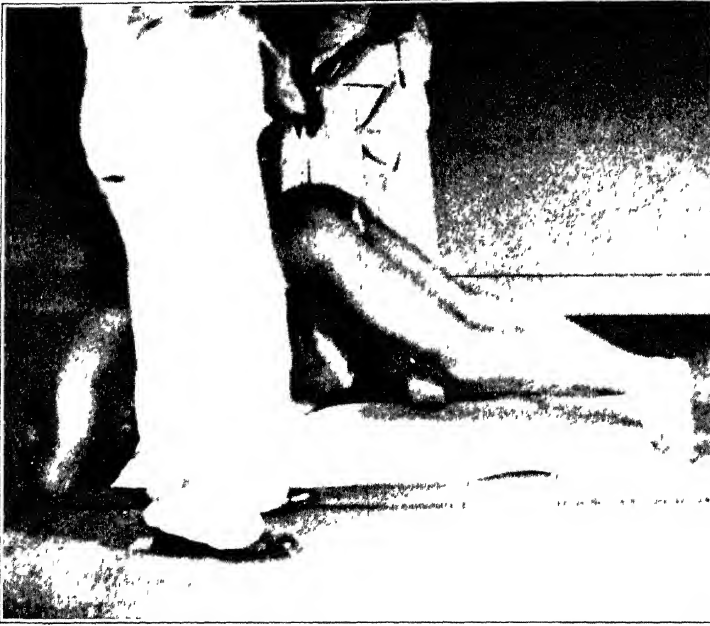
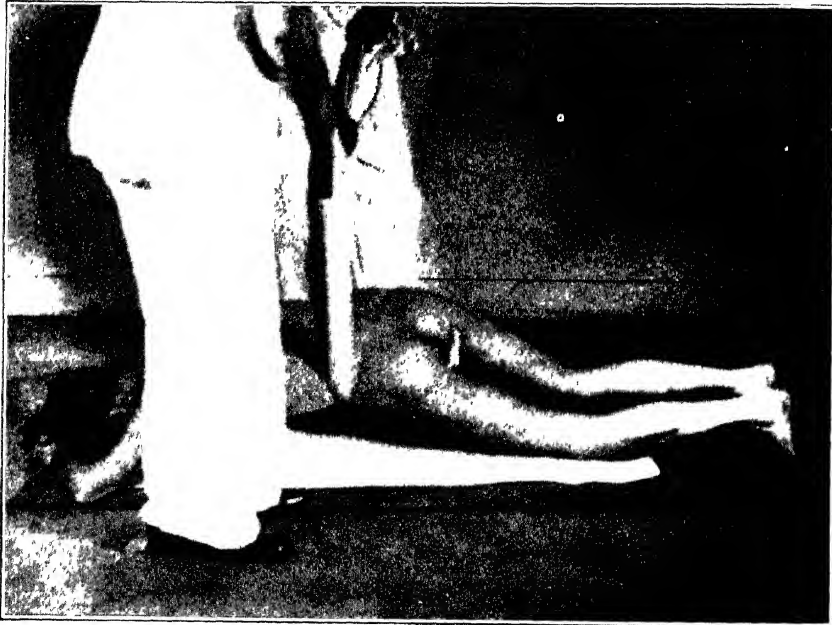
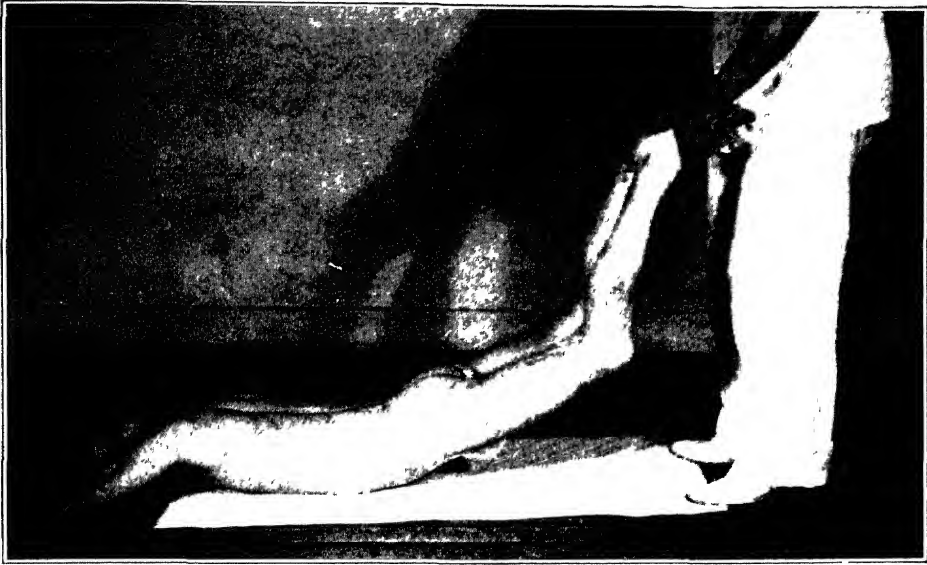
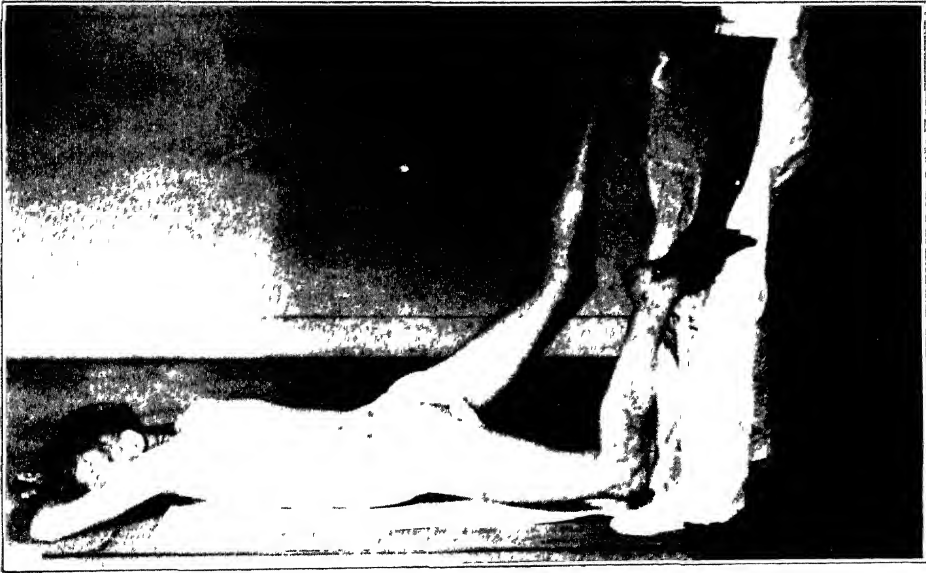
*A**B*

Fig. 11—Same procedure as shown in Fig. 10, using canvas strap when patient's weight is too much for long manipulator to manage. (F. A. Jostes, J. Bone and Joint Surg. (Oct.) 1938.)



A



B

Fig. 12- Maneuver 8—hypertension of spine plus rotation of pelvis first to left and then to right, with spine in hyperextension (Lumbosacral maneuver resulting in hyperextension plus rotation of joint). The legs are likewise moved from left to right so as to describe an arc in relation to the trunk. Has tendency to efface list by mobilizing lower thoracic and lumbar spine in lateral direction. (F. A. Jostes, J. Bone and Joint Surg. (Oct.) 1938.)

type of bedpan. He got out of bed by assuming the prone position, moving knees to the side of the bed, 1 foot was placed on the floor, the weight being carried on opposite knee by the hands. Use of the bedpan could be facilitated by placing it in an arm chair of the Windsor type. The subject could then lower and raise himself by placing his hands on the chair

arms. The hospitalization for the acute case was 2 to 3 days and for the chronic case 10 to 14 days. A back support was applied. The patient was instructed in measures to save his back, particularly in regard to driving a car, sitting and rising from chairs and picking up objects. He continued his hard bed and exercise régime.



Fig. 13 — Maneuver 9 — passive straight-leg raising (Modification of Baer's technic — counterclockwise rotary movement of sacroiliac joint) (F. A. Jostes, J. Bone and Joint Surg. Oct. 1938)

SCIATIC PAIN OF UNKNOWN ORIGIN

Treatment—When, after an exhausting clinical search, the etiology of an existing sciatic pain continues a mystery, G. F. Haggart⁷ recommended *infiltration of the piriformis muscle*, the region of the great sciatic notch and perchance the sheath of the sciatic nerve with up to 150 cc of 1 per cent novocaine. He found that 11 of 15 cases so treated were free from symptoms for an

average period of 20 months. In 27 cases the perineural injection was followed by 36 hours of 25 to 50 pounds traction to the leg by the Russell method. For the remainder of the 2 weeks a maintenance traction of 10 to 15 pounds was continued. Sixteen cases so treated were free from pain 1 year. In 23 cases the perineural injection was followed by a low back manipulation under general anesthesia. Nineteen had no recurrence of sciatica.

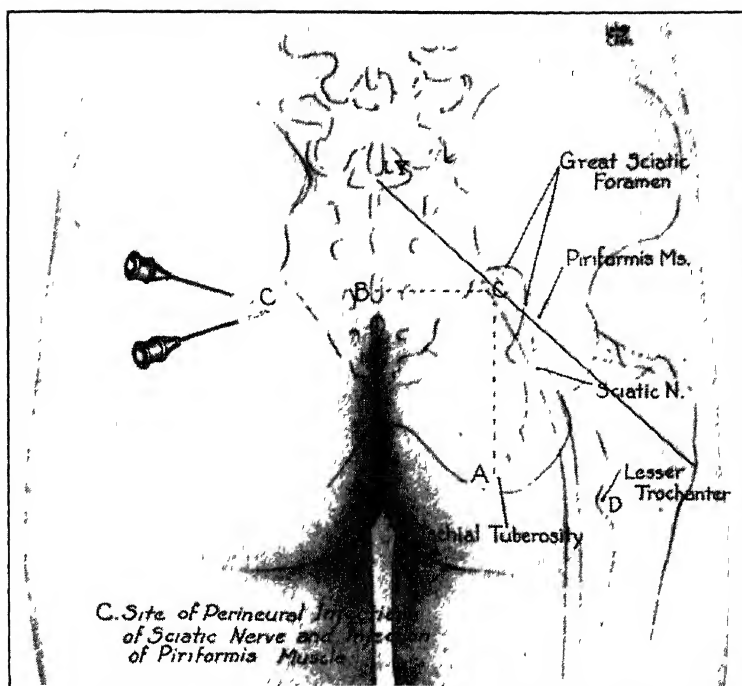


Fig. 14—Technic of perineural injection of the sciatic nerve as it emerges through the greater sciatic foramen. The intersection of the dotted lines and the line drawn from the femoral trochanter to the fifth lumbar spinous process indicates the point at which the needles are introduced (G. E. Haggart, *J. Bone and Joint Surg.* (Oct.) 1938.)

CHONDRODYSTROPHY WITH FLATTENING OF THE VERTEBRAE

Guerin and Lachapelle review the literature on chondrodystrophy with flattening of the vertebrae and report a case of their own of a boy aged 7 years. In *Rev. d'orthop.* 25:23, '38 the authors label the patient's condition as "platybrachyspondylie," since the vertebrae were large and flat. Each vertebra tended to end anteriorly in a pointed extremity, thus giving a moderate kyphosis. Roentgenograms of the entire body were taken and associated abnormalities of the skeleton were found. Both feet showed a hallux valgus. The first metatarsals were large and short, the second and third metatarsals curved medially, and in place

of the scaphoid and the first cuneiform bone there were several ill-defined centers of ossification. The second and third cuneiform bones were fused. There was a general retardation in the development of most of the skeletal epiphyses.

ACUTE OSTEOPOROSIS

Roentgenotherapy—E. B. Mumford⁶ reported a series of cases of posttraumatic osteoporosis or Sudeck's atrophy which were relieved of symptoms with roentgen therapy. The typical case followed a trivial injury such as a bruise or sprain to the wrist, hand or foot. Within a few days the subject complained of a severe, constant throbbing ache which was not relieved by heat or rest. The skin became

shiny. The hand or foot became swollen, cool and pale or blue. The joints were stiff. The roentgen film showed a thinned cortex, a mottled medullary cavity and uniform demineralization. The condition frequently persisted for months or even years. In using an x-ray, dosage suggested by Kahlmeter of $\frac{1}{4}$ to $\frac{1}{5}$ skin dose repeated 2 to 3 days, a second course in 4 to 6 weeks or a third in 6 to 8 weeks, 5 of 6 cases were completely relieved of symptoms.

OSTEOMYELITIS OF THE SCAPULA

Wilensky⁷ discussed osteomyelitis of the scapula and limits his cases presented to those caused by ordinary pyogenic lesions, such as staphylococcus, streptococcus, etc., and not to tubercle bacillus or spirocheti pallida. He classified this condition of the scapula into:

1. Primary osteomyelitis due to the production of open wounds extending down to and through the scapula.

2. Hematogenous osteomyelitis.

Pathogenesis and Pathology—The pathogenesis and pathology of this lesion is similar to that of other bones of the body and is based upon the formation of a thromboembolic lesion in the vascular plexus of the bone.

3. The lesions vary from inconsequential segments to involvement of nearly the entire anatomic segment

Symptomatology—The author gave the symptomology of the hyperacute, the moderately severe, and the mild cases, as well as a splendid résumé of the complications and sequelae that may follow osteomyelitis of the scapula.

Treatment—The treatment advocated was toward the conservative side, limiting the suppuration, the necrosis and sequestration. *Rest* was very essential and Wilensky favored *immobilization*

in a plaster cast. After sequestration is completed do a *sequestrotomy* on the severe cases. The author stated that if this treatment is followed there will be fair functional results provided there is not a large amount of disturbance in the shoulder joint.

OSTEOMYELITIS IN CHILDREN

Ober⁸ discussed the diagnosis and treatment of osteomyelitis. In acute osteomyelitis in children under 2 years of age the outstanding symptoms were acute sudden onset, marked constitutional reaction, high fever, rapid pulse, restlessness, loss of appetite, irritability, delirium and prostration. There was general tenderness localized to the affected part with swelling near the joint. The joint was held in flexion. The dry skin, sunken eyes, blueness of facies or extreme pallor indicated that these children were poor surgical risks. It was recommended that they receive generalized treatment, especially fluids, until an abscess formed beneath the skin and fascia. Then with a minimum amount of anesthesia an incision was drained and light cast applied with a window to facilitate dressing of the wound. By following this routine in the past 25 years the mortality has been reduced from 50 per cent to less than 5 per cent.

In children over 2 years of age the causative organism was usually staphylococcus instead of streptococcus. Because of the heavier periosteum and denser cortex, localization by pointing abscess beneath the skin was less common. The formation of sequestra was the rule. The x-ray changes could not be observed until 10 days to 2 weeks after the onset. The treatment depended upon the course of illness. In a very ill child, as described previously, opera-

tion was deferred until the general condition had improved. In a child who appeared in excellent condition in spite of high temperature, immediate operation was indicated. It was recommended that a button of bone be removed from the involved area and that the overhanging edges of the shaft be smoothed off.

Slow onset of symptoms with moderate local pain, slight temperature and leukocytosis were allowed to rest until the x-ray showed sequestra formation and adequate involucrum to permit removal.

Treatment—In chronic osteomyelitis 3 types were recognized. First, the sclerosing type which gave symptoms of a boring bone and was relieved by *drill holes at site of sclerosis*. Second type was Brodie's abscess which gave intermittent pain. This lesion was opened by *saucerizing the surrounding bone* and packing it with gauze. Frequently no organism could be cultured but usually staphylococcus was found. The continuation of an acute osteomyelitis formed the third type of chronic lesion. These were treated conservatively until the sequestra could be removed.

ACUTE HEMATOGENOUS OSTEOMYELITIS⁹

Robertson states that the most frequent types of hematogenous osteomyelitis are due to staphylococcal and streptococcal infections. The mortality in 337 cases was 22 per cent for staphylococcus and 13 per cent for streptococcus. Streptococcal osteomyelitis caused no necrosis of bone, was cured by drainage and had no sequels. Staphylococcal osteomyelitis, on the contrary, caused necrosis of bone with formation of sequestra; recurrence and exacerbation were frequent. The staphylococcus bacterium excreted an exotoxin. This was high in early growth

as proved from the culture plates. A toxin has 3 manifestations—leukocytolysin, hemolysin and necrotizing. This toxin in pure form caused death in experimental animals within a few hours. The resistance of an individual was dependent upon natural antitoxin and the destruction of the bacteria by phagocytosis. The toxin of the bacteria stimulated the antitoxin. This had an opsonic action in preparing the bacteria for ingestion by leukocytes. The antitoxin of the blood could be measured in antihemolytic units. Three hundred and five normal individuals of assorted ages at various times throughout the year were tested and found to have a titer under 1 unit. All types of surgical cases, other than pyogenic infections, showed no increase in titer. In 37 eruptive skin infections, however, there was a range of 0.1 to 6 titers, with an average of 1.36. If toxoid was given to the normal individual, the titer was raised 15 to 16 times. The lowest increase attained was above the greatest normal titer. If toxoid, the toxin element was destroyed, but the anergin factor remained. The effect of vaccines in raising the titer had not been tried.

It, therefore, appeared that a high degree of natural antitoxin would be an excellent defense against staphylococcal infection. Ninety per cent of the deaths in staphylococcal osteomyelitis occurred in the first 2 weeks. With the presence of natural antitoxin a neutralizing action would have been obtained. Clinical cases with staphylococcal infection showed various levels of antihemolytic action of their blood. The infection appeared to stimulate a defense by increasing the antitoxin in the blood. A natural high level of antitoxin in patients indicated a low general resistance. Prepared antitoxin, however, does not act as an antigen for production of natural antitoxin.

If antitoxin was given intravenously in the mild stages of the infection, it did not have the beneficial effect that was expected. Its use intramuscularly was still recommended. Following infection the high titer was not maintained. This was probably due to the fact that the antitoxin was not prophylactic but a neutralizing agent. It was advocated that 3 times the normal titer be maintained in chronic or healed cases. A regular investigation of the patient's blood was carried out and, if it was below 3, toxoid was administered.

The *prevention* of bone lesions depended upon giving children with skin lesions a course of *toxoid* if their titer was low and *limiting their activities* to prevent trauma.

The treatment was formerly immediate drainage. This was discredited, as surgery was thought to offer nothing until a state of equilibrium had been reached. The problem was one of combating infection by dealing with toxins and organisms, then drainage of abscesses after they had become well established.

BRODIE'S ABSCESS¹⁰

Brailsford analyzes a series of 62 cases of chronic bone abscess. The lesion occurred twice as often in the male as in the female. Forty-four cases occurred between 11 and 30 years. The younger the patient the shorter the duration of the symptoms. In nearly one-third of the cases the patient either exhibited evidence of previous septic bone foci or subsequently developed such lesions, while others gave a history of tonsillitis, pneumonia, empyema, etc.

Physical Signs and Symptoms—"The chronic abscess has an insidious onset, quite distinct from acute osteomye-

litis, in which the striking clinical features are the sudden onset of severe or even excruciating pain and the development of a point of tenderness over the primary focus, associated with rigors, high fever, and rapid pulse, followed by the signs of a severe toxemia, delirium and coma."

Radiographic Signs—"Acute osteomyelitis cannot be diagnosed by x-ray for by the time the bone shows changes detectable by radiography the shaft will have been denuded of periosteum and sequestra have formed. Chronic bone abscess at the diaphyseal extremity in the patient whose epiphysis has not yet fused is revealed on the radiograph by an area of cancellous destruction extending from the epiphyseal growth cartilage towards the medulla. Its boundaries are not sharply defined but are rendered more apparent because the adjacent bone has an increased density.

Differential Diagnosis --"There is perhaps no lesion in which the clinical history of the patient is more helpful in diagnosis than the Brodie's abscess." The author quotes Brodie's own words, "What are the circumstances that would lead you to suspect the existence of abscess of the tibia? The answer is, when the tibia is enlarged from a deposit of bone externally, when there is excessive pain, such may be supposed to depend on extreme tension, the pain being aggravated at intervals and these symptoms continue and become still further aggravated, not yielding to medicines or other treatment that may be had recourse to, then you may reasonably suspect the existence of abscess in the center of the bone."

The author differentiates Brodie's abscess from simple bone cysts, osteoclastoma, sarcoma, tuberculous abscess, gumma, and endothelial myeloma.

TUBERCULOSIS OF THE SPINE¹¹

Operative and Conservative Treatment—The authors reported a series of 43 cases, 26 being treated by fusion operations and 17 treated by conservative methods. All of the patients were under 20 years of age.

The criteria for cure were as follows:

"1. Pain, fever, muscle spasm, and body tilt must have disappeared for at least 3 months

"2 Abscesses must have disappeared, both clinically and roentgenologically, and sinuses must have been closed

"3 Roentgenographically there must be seen increased calcification in the area of destruction, and cessation of all advance of the tuberculous process."

It is interesting to note that the time for hospitalization of those treated conservatively averaged 876 days, while 1215 days was the average hospitalization for those treated surgically. The writers concluded that tuberculosis of the spine is a chronic disease which runs its course little influenced by the orthopedic surgeon.

Of the 26 patients treated by fusion operations the pathological process in the vertebrae was apparently uninfluenced by the operation although the fusions themselves were successful. Paraplegia developed in 4 of the cases following operation. There was no difference in the 2 groups in regard to an increase in deformity, since the condition progressed despite fusion.

Judging from the discussions following the article, the subject is a very controversial one. The fact is pointed out that fusion operations should not be used indiscriminately and their limitations respected.

ILIOPECTINAL BURSITIS¹²

As the author stated, iliopectinal bursitis is a rather frequent lesion but the

unfamiliarity with early symptoms causes the condition to be classified erroneously many times. Finder reported a case of this bursitis in a man at the age of 49 years. The history and symptoms were fairly typical of hypertrophic arthritis, the right hip joint being particularly troublesome. During the examination a swelling the size of a lemon was noted in the right inguinal region. This rapidly grew larger. Nine years later the patient was admitted to the hospital with a diagnosis of advanced Bacterew type of spondylitis deformans. Both hips were contracted in 35 degrees flexion. In the right groin a firm semisolid tumor, the size of a large grapefruit, elevated and displaced the femoral sheath and its contents medially. X-rays confirmed the diagnosis of arthritis of the spine and hips. The tumor in the groin cast a slight shadow (soft tissue). On the basis of the large tumor, loss of weight, secondary anemia, cough, etc., the diagnosis was made of fascial sarcoma of the right inguinal region with metastases to the lungs. This, however, was discarded as the tumor was aspirated a few days later. Then an exploratory operation was performed and it was found that in the lateral portion of the floor of the sac was a tiny valve-like flap overlying a 3 to 4 mm opening which communicated with the hip joint. When the hip was passively moved, synovial fluid was seen to pass from the joint through the opening into the sac cavity. The communicating tunnel and the adjacent portion of the bursal floor were resected and the capsule was sutured tightly across the defect so as to obliterate the passage between the joint and the bursa.

Two and one-half months after the operation there was no sign of re-establishment of the communicating with the hip joint.

MYOSITIS OSSIFICANS

C. F. Geschickter and I. H. Maseritz¹³ found in the circumscribed myositis ossificans that trauma was the most frequent cause. The severity of the injury could not explain the reaction which might follow an initial mild blow or multiple severe blows. The thigh was the most



Fig. 15—The so-called "dotted-veil" appearance in an advanced case of myositis ossificans. (Courtesy, *Journal of Bone and Joint Surgery*, July, 1938.)

common site but the disturbance was particularly prone to occur following dislocation or fracture dislocation of the elbow. Occupations, such as shoemaker, rifleman or horseman, played no part. The ages ranged from 13 to 72 years. The earliest clinical finding was a doughy mass which appeared within a few hours following injury. In 3 to 4 weeks the x-ray revealed small discrete, dense shadows which were likened to the "dotted-veil."

Pathology—Pathologically the lesion was surrounded by a gelatinous material representing degenerated muscle tissue which was absent at the attachment to bone. There was a fibrous capsule which was penetrated by fibrous bands of connective tissue which invaded the new bone formation from the neighboring bone. Cystic changes were occasionally found that resembled giant cell tumor formation. Microscopically the earliest manifestations were a degeneration of muscle, a hyperplasia of connective tissue and organization of hemorrhage. The capsule formed simultaneously with the calcification. Islands of osteoid tissue appeared and were surrounded by osteoblasts. Then marrow spaces formed. An appearance of osteogenic sarcoma was created by areas in which osteoblasts were attempting to form bone in an osteoid-like stroma. Chondromyxosarcoma was suggested by the myxomatous-like tissue which was found.

Treatment—The treatment of myositis ossificans circumscripta was conservative. Attempted surgical removal was followed by frequent recurrences if done before the lesion had shown no change by x-ray for 6 months, or if the removal had been incomplete. Deep roentgen therapy had no proven value. Occasionally there was a spontaneous regression of the process.

RUPTURE OF THE BICEPS BRACHII MUSCLE

R. L. Waugh¹⁴ reported a series of 14 cases admitted to the United States Marine Hospital in San Francisco and to the New Orleans Hospital and Dispensary for Women and Children. The author stated that rupture of the brachii muscle is not uncommon but is very often unrecognized. Twelve of the 14

cases had a rupture of the long head of the biceps muscle, but rupture may occur at any site. In injuries caused by direct trauma, rupture below the bicipital groove was common. From the report of the 14 cases the signs and symptoms varied, but there was always a history of trauma followed by pain, weakness in the arm and discomfort in the shoulder. However, the most constant sign was a deformity in the contour of the biceps muscle. Waugh did repairs on 12 of the 14 patients. He stated that rupture of the long tendon was the easiest repaired. If there was a tear at the myotendinous junction, a fascial transplant was necessary. In the patients sustaining a partial rupture of the biceps brachii muscle, the author advised rest with the tendon in a position of relaxation.

SCALENUS ANTERIOR MUSCLE

Relation to Shoulder and Arm Pain

This was reported by J. A. Freiberg¹⁵ In 1935 Ochsner, Gage and DeBakey reported a series of cases presenting a clinical picture of cervical rib in which no cervical rib could be demonstrated. The condition was termed "scalenus anticus (Naffziger) syndrome." This condition had been described by Todd in 1912 who believed it due to an abnormal development of the shoulder girdle. This was particularly true in women who presented a greater shoulder descent. The scalenus anticus syndrome was found to be more complicated and to have more intimate associations with other shoulder lesions. The clinical picture of such common pictures as calcification of the supraspinatus tendon, subacromial bursitis, periarthrititis of the shoulder or cervical arthritis were accompanied with pain,

paresthesia and numbness of the lower arm and hand. These symptoms were explained anatomically. The scalenus anterior muscle arises from the transverse processes of third, fourth, fifth and sixth cervical vertebrae and inserts into the anterior third of the first rib. Its action is to flex the cervical spine when the rib cage is fixed and to elevate the rib when the cervical spine is maintained in extension.

The subclavian artery lies between the scalenus anterior muscle and the first rib. The sixth, seventh and eighth cervical nerves are in close relationship to it. The third, fourth and fifth cervical nerves lie beneath the scalenus anticus muscle and are less frequently involved than the former group. Spasm of the muscle may result in a variable amount of pressure on the cervical roots lying behind it. Symptoms are manifest which are associated with cervical or supernumerary ribs. Innervation of the scalenus anterior muscle is derived from the seventh cervical root, therefore, its irritation by contracture of the scalenus anterior muscle caused a vicious cycle. In a series of 20 cases, those cases subjected to tenotomy were all relieved of symptoms. Conservative therapy, consisting of maintaining the arm in abduction with traction on both shoulders, usually gave relief. However, in 1 case of a fireman with excruciating pain which existed for 10 days, scaleniotomy gave immediate relief. The presence of muscle atrophy and muscular disturbance was an indication for immediate scaleniotomy.

STENOSING TENDOVAGI- NITIS AT THE RADIAL STYLOID PROCESS

DeQuervain's disease or stenosing tendovaginitis as described by H. B. Keyes¹⁶ was due to a stenosing fibrosis

of the conjoined tendon sheath of abductor pollicus and the extensor pollicus brevis tendons over the radial styloid. It occurred in subjects that used their hands in constant repetition of motion which required ulnar deviation of hand with thumb extended. It was common in piano players, stenographers, and writers. The pain was in the region of the radial styloid. It radiated to the thumb. It was accentuated by actions which opposed the thumb to the finger tips. There was acute tenderness over the radial styloid. The concavity of the anatomical snuff box was obliterated. If the hand was grasped with the thumb extended and forced toward the ulnar side, excruciating pain was produced.

Treatment of a conservative nature, as splints to hold the thumb in extension and abduction, heat, etc., was seldom successful. Dramatic results followed a *longitudinal division of the conjoined tendon sheath* through its thickened and stenosed area to release the constriction on the extensor pollicus brevis and abductor pollicus tendons.

CONGENITAL DISLOCATION OF THE HIP

Mechanics of the Formation of the Secondary Acetabulum

A. Farkas¹⁷ of Budapest in an article on congenital hip stated that dislocations difficult to reduce are of a "true congenital" nature. He examined the mechanics of the formation of the secondary acetabulum from children of the Brody Children's Hospital and found that "in the so-called congenital cases the secondary acetabulum has a well-shaped lower border; in the true congenital cases, a well-shaped upper border. In the former, the head forms its socket by gliding and rubbing; in the latter, by direct pres-

sure." The reason for this difference in the location of the definitely formed border is evident since in the so-called congenital hip the gliding head has but 1 fixed point from which it starts during the movements of walking, etc., and to which it returns and remains during rest, while in the true congenital hip the boring head cannot extend beyond its upper border, which is firmly formed in the embryonic stage. During all movement the head returns to this area and by its constant pressure the groove is increased. The author found that in all cases with a deep groove and a well-developed upper and lower border of the secondary acetabulum, reposition of the head was either very difficult or else impossible. He stated that the true congenital cases are in a great minority and agreed with Lorenz that all cases in which dislocations occur before birth are of a teratoid nature and that they occur very infrequently.

Congenital Dislocation of the Hip in the Newborn

V. O. Marks¹⁸ reported a series of 8544 births in Kharkov in 1937. He stated that congenital dislocation of the hip was found in 1 per cent of the normal births and in 11 per cent of the breach presentations. Out of a group of 194 children with congenital dislocation, spontaneous reductions were noted very early in life in 47.4 per cent. However, Marks stated that the disappearance of clinical and x-ray evidences of dislocation in early life may not coincide with definite reduction. He advocated the early application of a duraluminum apparatus, and, even though reduction appeared to have taken place in the first few weeks of life, the children were kept under observation for a period of 2 to 3 years.

SPINA BIFIDA OCCULTA

H. F. Buchstein and J. G. Love¹⁹ conclude that spina bifida occulta is a developmental defect of the spinal cord, its meninges, the vertebrae, and the overlying muscular and cutaneous tissues. This begins in early embryonic life. The clinical symptoms are usually the result

of neural dysfunction. The most common symptoms are related to the urinary apparatus. Motor, sensory and trophic disorders about the lower extremities are common and should arouse suspicion of spina bifida occulta. Once it is suspected it is easily verified. The surgical treatment is *laminectomy*.

OBSTETRICAL SHOULDER TRAUMA

Putti, according to Scaglietti,²⁰ classified birth palsy as follows:

1. Obstetrical trauma of the shoulder joint.
 - (a) Simple: distortion
 - (b) Complicated epiphyseal separation of upper end of humerus.
 - (c) Fractured clavicle.
2. Obstetrical paralysis
 - (a) Upper type
 - (b) Lower type
 - (c) Total type
 - (d) Associated atypical form
3. Mixed forms involving both joint and nerves

In a series of 199 cases there were 62 cases of shoulder joint involvement. The diagnosis of this lesion was important. There was a fracture through the cartilaginous epiphysis above the epiphyseal line. This explained the absence of hematoma and periosteal callus. The lesion healed with an extreme internal rotation of the humeral head so that the joint surface was posterior. This position was favored by the natural tendency for the child to splint the arm in adduction and internal rotation.

Treatment—The treatment during the first 2 years of life was to prevent internal rotation contracture by holding the arm in 60 to 70 degrees *abduction* and *full external rotation*. After cor-

rection had been obtained with 2 or 3 successive plaster shoulder spicas a brace was applied to maintain the position and heat, massage and exercise started.

After the second year of life the deformity was corrected surgically. This



Fig 16—Four-year-old boy. Forceps delivery. Atrophy of right shoulder muscles. Internal rotation of arm. Shortening of 1 centimeter. By adducting the arms (adduction on right side diminished) the vertebral margin of the scapula is brought almost into a sagittal plane. (Scaglietti Surg, Gynec and Obst (May) 1938)

was best accomplished by the capsulotomy and release of internal rotators devised by Sever and the external rotation osteotomy through the surgical neck recommended by Putti.

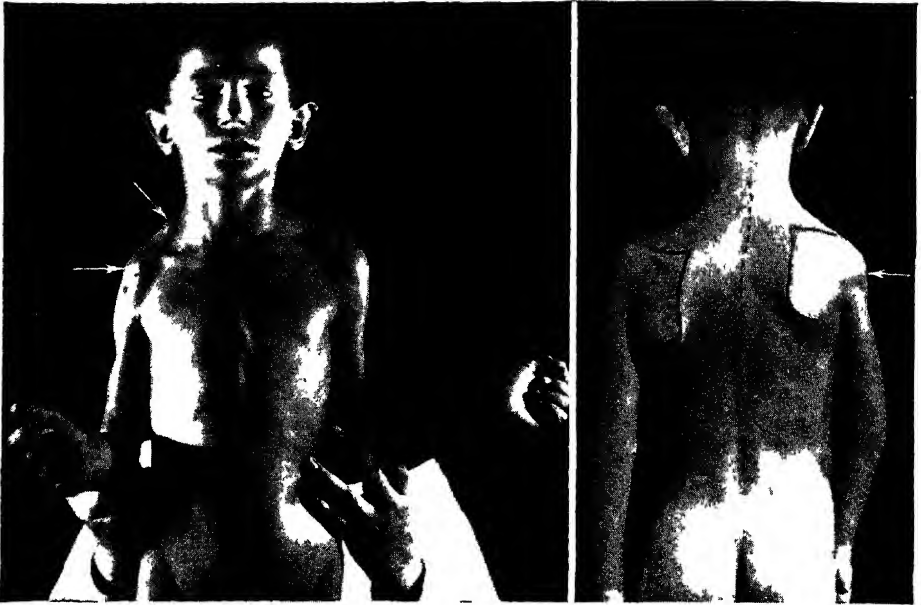


Fig 17—Eight-year-old boy Forceps delivery No external rotation on right Putti's scapula sign well visible Loss of normal shoulder relief Coracoid process strongly prominent (Scaglietti Surg, Gynec and Obst. (May) 1938)

Fig 18—Same case as in Fig. 17 Scapula high and hypoplastic Abduction and internal rotation of right arm which is considerably shorter. Beginning left convex scoliosis. (Scaglietti Surg, Gynec and Obst (May) 1938)

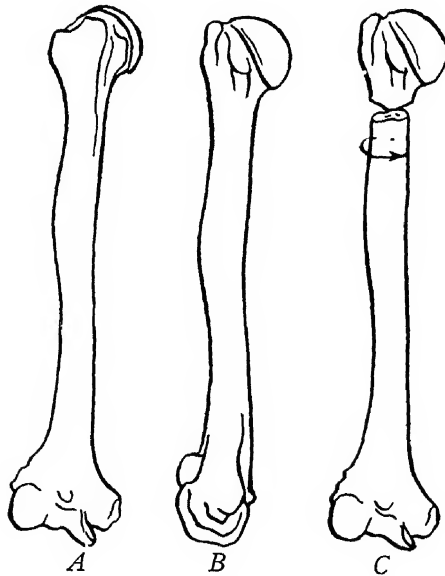


Fig 19—Humerus after obstetrical shoulder trauma. A—Neutral rotation, epiphysis in retroposition B—Complete external rotation, epiphysis is in normal contact with glenoid C—Rotation osteotomy of Putti to bring the lower end of the humerus in a frontal plane (Scaglietti. Surg, Gynec and Obst. (May) 1938)

GONOCOCCAL ARTHRITIS

W. W. Spink and C. S. Keefer²¹ emphasized the importance of history, smears and cultures together with positive gonococcal complement fixation tests of either blood or synovial fluid and the gonococcal organism and aspirated contents of joints. Cases were divided into 3 groups according to treatment.

Group 1 was treated medically with general measures; 11 received vaccines—typhoid paratyphoid 15,000,000 organisms increased 25 to 50 mg. for 5 doses. There was a total of 26 cases in this group with an average hospitalization

of 50 days. Two died. Eighteen were free of joint symptoms.

Group 2 was treated by aspiration. All cultures were sterile except in 1. There were 22 cases in the group, with an average hospitalization period of 53 days. Fourteen had complete return of joint motion.

Group 3. Those receiving surgical drainage had the joints washed with saline or 1:10,000 solution bichloride of mercury. All wounds closed tightly. There were 20 cases in the group with total hospitalization of 61 days. Only 3 had return of function.

ARTHROPLASTY OF THE HIP²²

Fuiks reported a series of 57 patients on whom arthroplasty of the hip had been performed for various causes—3 of the patients undergoing bilateral arthroplasty, making a total of 60 hips. Table 1 gives the end results according to pathologic conditions

Table 2 shows the results of arthroplasty classified according to age group.

Table 3 gives the results of arthroplasty classified according to postoperative observation

Table 4 shows the results classified according to operative technic.

Fuiks summarized his article by saying the "Uniformly poor results followed bilateral arthroplasties of the hip (3 cases) Results cannot be classified as failures merely because pain is present during the first year, as this is quite common, especially in cases of hypertrophic arthritis The best results were obtained in cases in which sclerotic bone existed, such as suppurative arthritis, osteomyelitis, hypertrophic arthritis, and gonorrheal arthritis The

TABLE 1
CLASSIFICATION OF END RESULTS ACCORDING TO PATHOLOGIC CONDITIONS

Diagnosis	Bilateral Arthroplasty	No of Arthroplasties	Good Results		Fair Results		Failure	
			No of Cases	Per-centage	No. of Cases	Per-centage	No of Cases	Per-centage
Hypertrophic Arthritis	1	15	7	46.66	6	40.0	2	13.33
Atrophic Arthritis	2	21	4	19.5	8	38.09	9	42.85
Suppurative Arthritis	0	9	4	44.4	3	33.3	2	22.2
Slipped Epiphysis	0	4	1	25.0	2	50.0	1	25.0
Congenital Dislocation	0	3	0	0.0	0	0.0	3	100.0
Osteomyelitis	0	3	1	33.3	2	66.6	0	0.0
Aseptic Necrosis	0	1	1	100.0	0	0.0	0	0.0
Gonorrheal Arthritis	0	4	3	75.0	0	0.0	1	25.0
Total Cases	3	60	21	35.0	21	35.0	18	30.0

(Courtesy, Archives of Surgery, March, 1938)

TABLE 2
RESULTS OF ARTHROPLASTY CLASSIFIED ACCORDING TO AGE GROUPS

Age at the Time of Operation	No. of Operations	Good Results		Fair Results		Failure	
		No. of Cases	Per-centage	No. of Cases	Per-centage	No. of Cases	Per-centage
0-13 Years	4	0	0 00	3	75 00	1	25 00
14-20 Years	12	5	41 66	3	25 00	4	33 33
21-30 Years	20	10	50 00	6	30 00	4	20 00
31-40 Years	7	1	14 28	1	14 28	5	71 42
41-50 Years	10	2	20 00	5	50 00	3	30 00
51-60 Years	7	3	42 85	3	42 85	1	14 28
Total Cases	60	21	35 00	21	35 00	18	30 00

(Courtesy, Archives of Surgery, March, 1938)

TABLE 3
RESULTS OF ARTHROPLASTY CLASSIFIED ACCORDING TO POSTOPERATIVE OBSERVATIONS

Time Since Operation	No. of Operations	Good Results		Fair Results		Failure	
		No. of Cases	Per-centage	No. of Cases	Per-centage	No. of Cases	Per-centage
6 Months-1 Year	5	2	40 00	2	40 00	1	20 00
1-2 Years	10	5	50 00	3	30 00	2	20 00
2-3 Years	10	5	50 00	4	40 00	1	10 00
3-5 Years	7	1	14 28	4	57 14	2	28 57
5-10 Years	18	6	33 33	5	27 77	7	38 88
10-20 Years	10	2	20 00	3	30 00	5	50 00
Average Postoperative Observation Time	60	21	35 00	21	35 00	18	30 00

(Courtesy, Archives of Surgery, March, 1938)

TABLE 4
RESULTS CLASSIFIED ACCORDING TO OPERATIVE TECHNIC

Type of Interposed Tissue	Total Cases	Good Results		Fair Results		Failure	
		No. of Cases	Per-centage	No. of Cases	Per-centage	No. of Cases	Per-centage
Fascia	53	20	37 73	17	32 07	16	30 19
Other Tissues	7	1	14 28	4	57 11	2	28 56
Total Cases	60	21	35 00	21	35 00	18	30 00

(Courtesy, Archives of Surgery, March, 1938)

hardness of the bone may be an essential factor to a good end result. Perhaps a synostosis could be considered as a good omen. After mobilization has been started, a frame allowing active abduction and flexion while in traction has been of value. Unsatisfactory results were obtained in cases in which operation was performed before epiphyseal arrest

occurred. Atrophic arthritis and congenital dislocations were the basis of the highest percentage of unsatisfactory results. The failures were not due to variations in operative technic. Results, on the whole, were not dependent on the age of the patient but rather on the pathologic condition for which operation was performed.

COXA PLANA

First Stages — H. Waldenstrom²³ emphasized the early recognition of coxa plana. This was done by the first symptoms which were limp and slight pain, commonly referred toward the knee. The

early signs were not noticeable to the eye but a limp was detected by the variance in gait when the patient walked across the floor with shoes on. At that time restriction of mobility of the hip was sufficiently noticeable to be measured

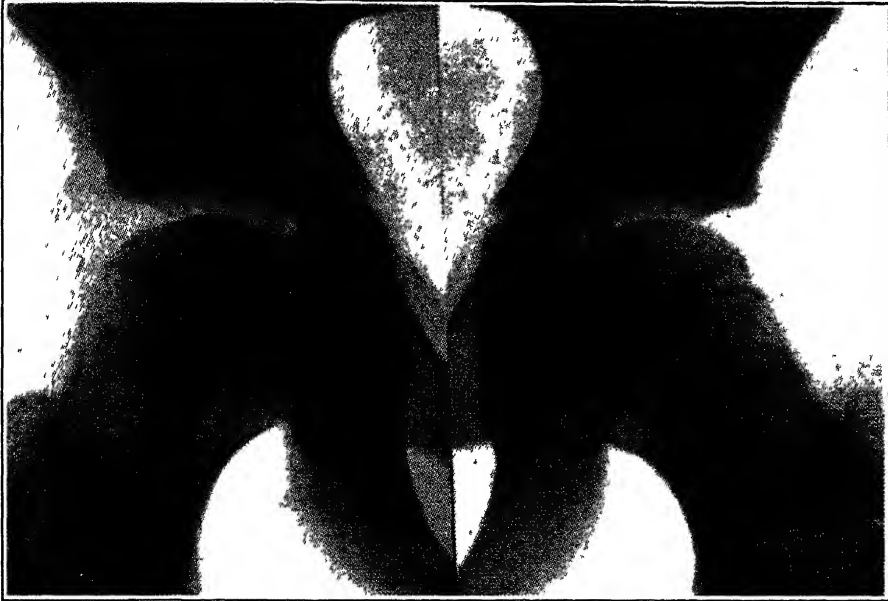


Fig 20

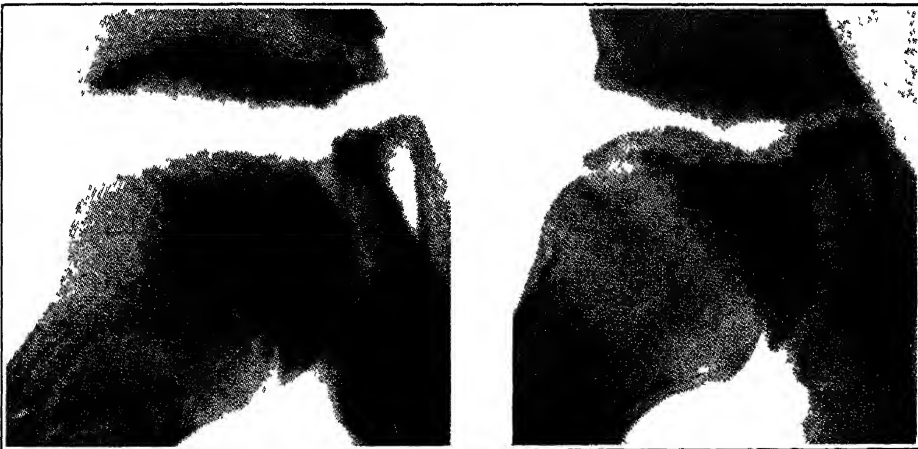


Fig 21

Fig 22

M-n, a boy, aged 9 years, was admitted to the hospital on September 6, 1932, with a slight limp of 3 months' duration

Fig 20—Roentgenogram, taken on admission, showing the epiphysis of the right femur to be lower than that of the left and flattened on its upper portion, as well as an increase in the distance between the epiphysis and the bottom of the acetabulum.

Fig 21—Lateral view (Lauenstein's position), taken on admission

Fig 22—Lateral view, taken one year later

(Courtesy, J Bone and Joint Surg (July) 1938)

in degrees when compared with the opposite hip. The x-ray pictures taken in the anteroposterior direction were normal. The lateral pictures (Lauenstein's position—femur in flexion and abduction) showed some changes. These were apparent in the femoral epiphysis. The epiphysis on the involved side was lower and there was a distinct flattening of the part facing the roof of the acetabulum. This flattening involved the upper anterior part of the epiphysis. At times it was visible in the roentgenogram due to the absorption leaving a thin narrow margin of bone along the cartilage, beneath which was an area of decreased density caused by the subchondral resorption of bone.

The disproportion in the size of the hip socket, as pointed out by Jansen in July 1929, did not occur in the early stages. This disproportion was due to a primary fault of the acetabulum or to the actual deformity of the head itself. This conclusion was based upon the x-rays of cases which had a bilateral coxa plana in which the second hip joint did not become involved until a year after the first. In none of these instances had the films taken during this year prior to the involvement of the second hip show any changes either in the acetabulum or the hip itself. Operative treatment of the coxa plana was definitely contraindicated. The drilling of the epiphyseal cartilage had not been tried. The other treatment was revised in a footnote, due to the recent acquaintance with the results which Dr. Murray S. Danforth of Providence had obtained with bed rest for a year or more.

POLIOMYELITIS

Physiological Rest in the Early After Care—According to C. T. Irwin²⁴ adequate rest in the convalescent polio-

myelitis case was frequently neglected. Rest did not merely imply confinement to bed but physiological rest of the involved muscles. Every surgeon recognized the imperative value of a cock-up splint for the wrist and fingers in a paralysis of the radial nerve. The identical principle of relaxation of the paralyzed muscle groups to give them rest had to be employed in poliomyelitis. A mechanical support had to be tailored to the patient. *Plaster of Paris bandages* or *splints* were the most practical and least expensive. Splints which fitted poorly produced more deformities than they prevented.

In application of the splint, correct positions were determined by the location and degree of muscle damage, the pull of gravity, and normal weight bearing lines. An extremity was supported to provide relaxation for the involved muscles and oppose the contraction of the uninvolved antagonist muscles. When the antagonistic muscles on either side of the joint were equally involved, the muscle most important in performing functions natural to the extremity was favored. The calf and posterior thigh muscles were of greater importance in the leg than dorsiflexors of the foot or the quadriceps, as a lower extremity in calcaneus and back knee was a poor one for locomotion. The biceps in the arm was of greater value than the triceps, as it was necessary to flex the forearm against gravity whereas extension would result from gravity.

Frequently immobilization was necessary because of myalgia before an analysis of muscle involvement could be determined. The optimum position obtained with the patient on his back on a firm mattress supported by boards over the springs, the arms abducted and externally rotated, the knees slightly flexed with a small pillow behind them, and the

feet supported by a box. Later the lower extremities were immobilized in plaster bandages with the feet in slight equinus and neutral to eversion or inversion. The knee and ankle joints were fixed in the same vertical plane with the knees

forearms in a position neutral to supination and pronation. Particular care was given to thumb, which was fixed abducted from the index finger and rolled toward the palmar surface of the hand with its tip toward the little finger.

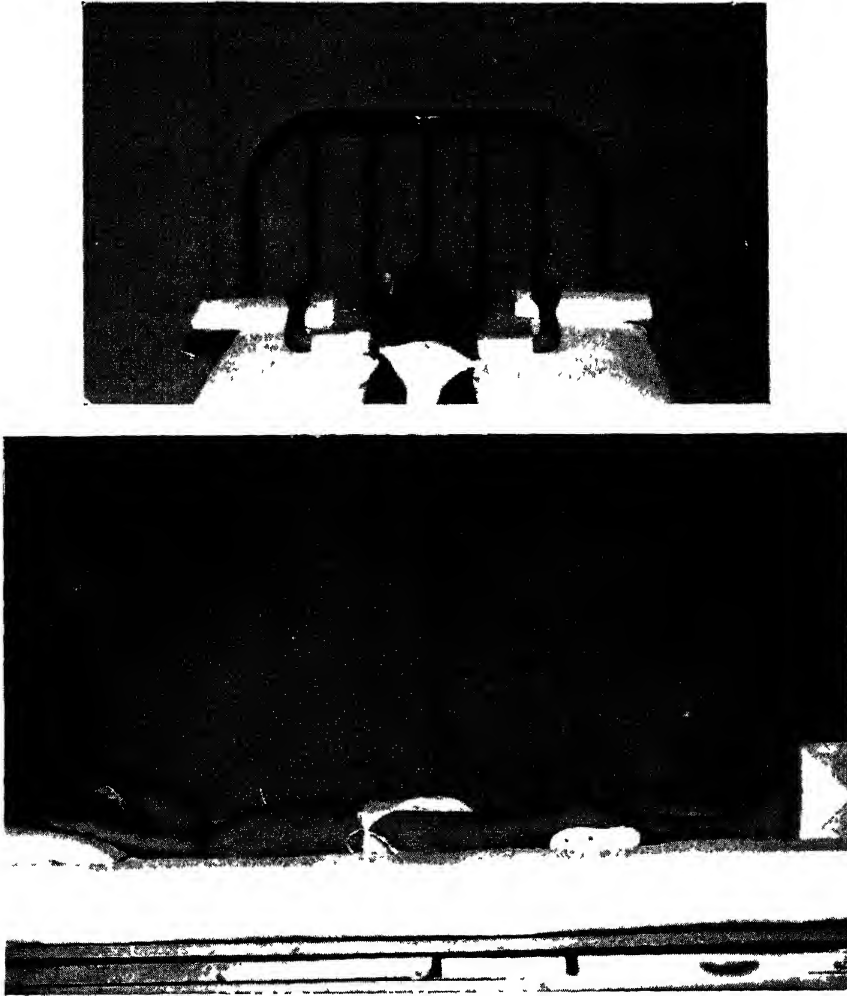


Fig. 23—Correct position for bed rest before any support is applied. Board has been placed between springs and mattress. Note position of arms, back, knees, and feet. (Courtesy, Southern Surgeon, April, 1938.)

flexed 10 to 15 degrees. The legs were held in some abduction and internal rotation. The abdominal muscles in cases with respiratory involvement were splinted by a body support or corset to prevent overactivity of the diaphragm and stretching of abdominal muscles. The upper arms were supported in abduction and the

Experience was necessary in supervision of cases as much that had been gained by rest can be destroyed in 5 minutes of careless handling of an extremity or in applying or removing splints. A series of passive motions could stretch out the few muscle fibers remaining intact. Tearing of muscle fibers and

interfibrillar bands resulted in hemorrhages which organized in the fibrous scar. Muscle pain caused the patient to assume unfavorable positions which resulted in "stretch paralysis" of relaxed muscle groups and contraction of antagonists. No fixed rules of treatment

rotation of vertebrae which accompanies the lateral curves, and by the obscurity which surrounds its causation and pathology. The last feature has given rise to the synonym of idiopathic scoliosis in contrast to curvatures associated with recognized pathological conditions, such

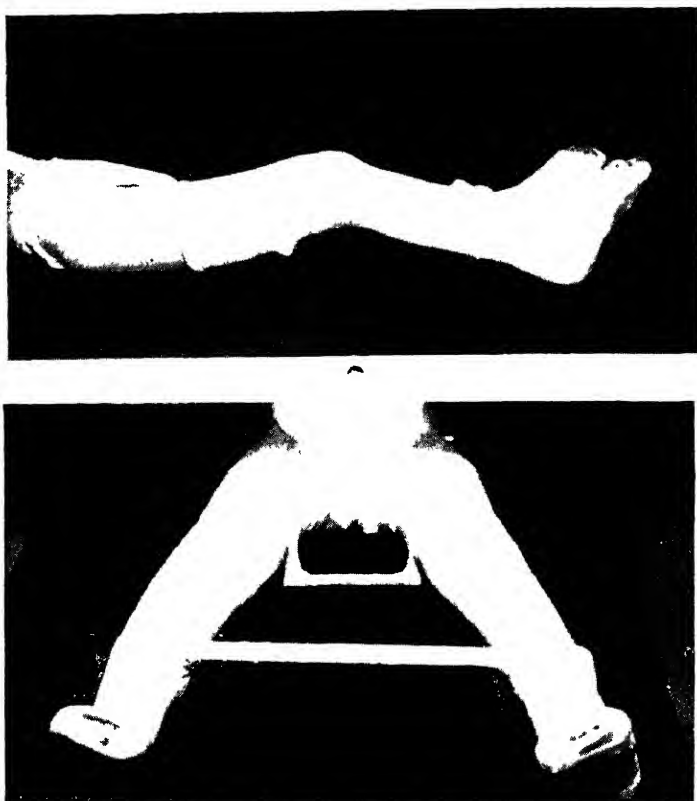


Fig. 24—Lower extremities immobilized in optimum positions. Note slight flexion of knees, mild equinus of feet, and abduction and internal rotation of thighs at the hip. These positions overcome the pull of gravity and favor the muscle groups behind the thigh and calf. These posterior groups are most important in weight bearing either with or without support. (Courtesy, Southern Surgeon, April, 1938.)

applied to all cases. Exercises were started in the convalescence, depending on the individual case. They were best given in a tank of warm water.

ADOLESCENT SCOLIOSIS²⁵

Pathology—"Adolescent scoliosis is distinguished from other forms of scoliotic curvature by its incidence among young girls, by the special tendency to

as congenital malformation of vertebrae, paralysis of spinal muscle groups, or contractures following intrathoracic disease."

The author gave the etiology of affecting girls more than boys, and of being associated with the approach or establishment of puberty. It is interesting to note that in the social incidence, scoliosis is much more prevalent in the carefully tended children. In fact it is rare among the neglected children of the

very poor. Therefore it is not a deprivation disease but appears to be associated with too anxious and solicitous an upbringing.

In the form of the curvature most usually seen the predominant curve and rotation are to the right in the dorsal region, with a subsidiary curve to the left in the lumbar region. The abnormal posture is more noticeable in the neighborhood of the right shoulder. The author stated that the reason for this was that the particular posture given above is especially expressive and that in the expressive gesture it is the upper right limb that is usually called into play. It is the right hand that is waved, the right fist that is clenched. In a left-handed girl suffering from scoliosis, the curve is to the left in the dorsal and the right in the lumbar.

Treatment should be directed to both the body and the mind since there is a psychological element attached to the scoliosis. The less said about the curve the better. The author believed that the best method of treatment for postural curvatures was to disregard the individual curves and rely on *free-standing exercises* under a judicious and well-trained instructress. The object of the exercises is to give confidence and to improve the bodily poise. It is essential that the exercises be enjoyable.

Abercrombie summarized the article by saying that the posture and deformity of adolescent scoliosis have an affinity with the attitude of bashfulness. This attitude is the expression of the modesty of puberty, it is defensive in origin, and is dependent on an ancestral postural reflex.

CEREBRAL PALSIES

Care and Treatment—W. M. Phelps²⁶ explained the general care of

the spastic child. This called for a correlated program by the orthopedist, pediatrician, neurologist, physical therapist, the speech expert and by teachers accustomed to adjusting the handicapped to their problem. A very careful analysis of these subjects was necessary to differentiate between the true mental deficiency and mental retardation due to handicap. The latter were much greater in numbers than the former.

Cerebral palsies resulted from congenital defect. Birth trauma and encephalitis were of 2 general types: (a) Those with damage to the cortex of the brain which had spastic paralysis, and (b) those with damage to the base of the brain which had athetoid paralysis. A combination of the 2 was rare.

The neurological examination was different in the 2 conditions. In a spastic paralysis a pyramidal lesion was indicated by hyperactive biceps, triceps, quadriceps and achilles reflexes, positive Babinski sign, ankle clonus and diminished or absent abdominal and cremasteric reflexes. In an athetoid paralysis the reflexes were normal. The speech defect when present was entirely different. In spasticity the defect was uniform, while in athetosis the involuntary motions never coincide with the voluntary so that a repetition would result in a different fault each time.

The plan of training varied in the 2 types. The spastic child could be taught alternation of movements and trained into habits by repetition. The athetoid child could not be trained by repetition as the voluntary movements were hampered by involuntary movements. This child had to be taught relaxation as in sleep before alternate movements could be performed. In either case attempts were made to have the child develop according to its mental and physical age.

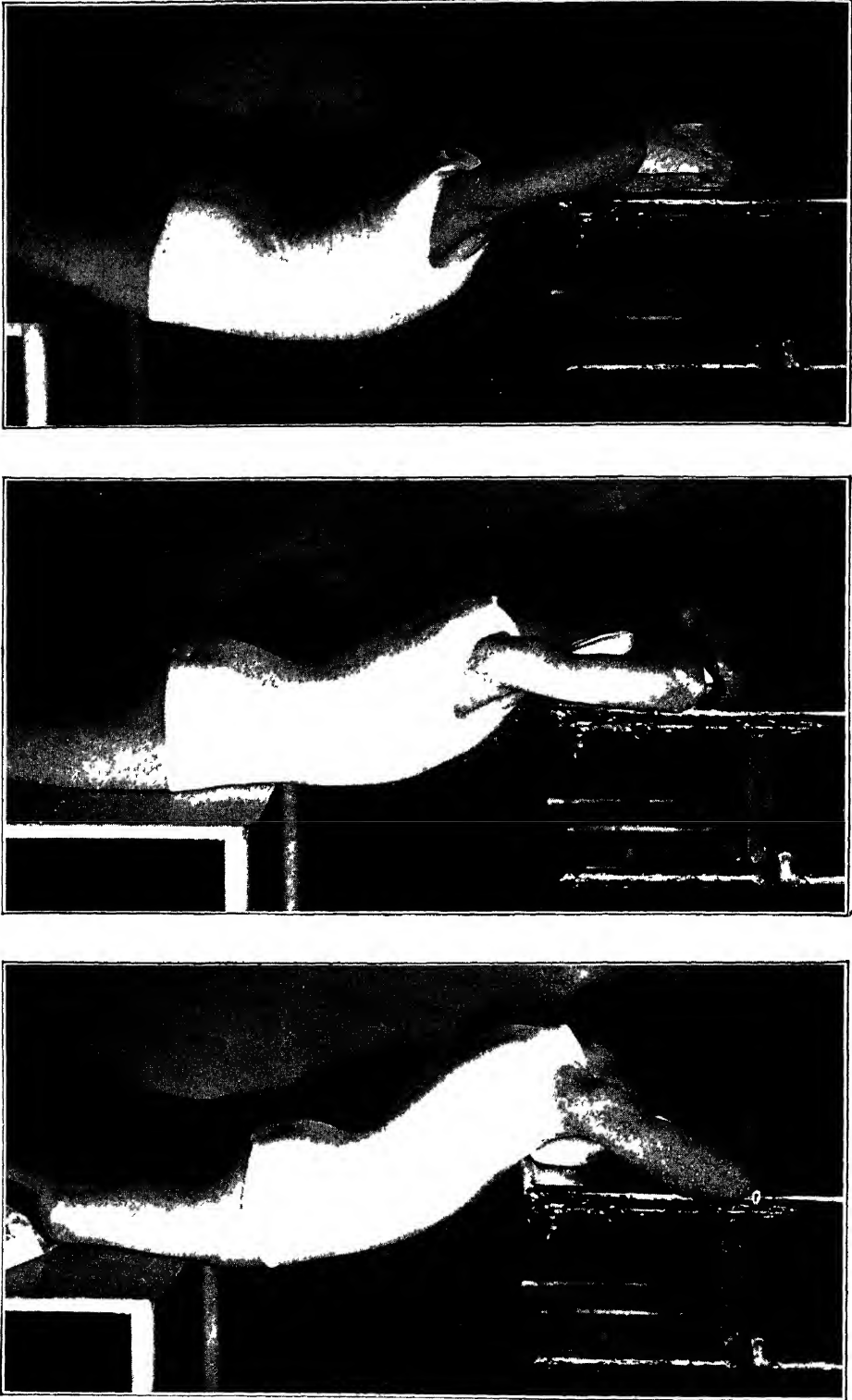


Fig 25—*Upper*—Correct position for postural reduction *Middle*—Incorrect position The lower table extends beyond the groins and prevents the pelvis from tilting forward The lumbar spine is incompletely extended *Lower*—Incorrect position The patient is too close to the upper table The thoracic spine is incompletely extended and the jacket cannot be carried high enough. Displacement will recur. (Watson-Jones J. Bone and Joint Surg (July) 1938)

almost always seen at the attachment of the anterior longitudinal ligament but was not considered a source of pain or arthritic change. Eighty per cent of the 67 cases of wedge or comminuted fractures resumed their original employment;



Fig 26—Correctly applied plaster cast, extending from the groins and the symphysis pubis to the clavicles. The lumbar spine cannot be flexed (Watson-Jones' J Bone and Joint Surg (July) 1938)

48 per cent of them were engaged in heavy labor.

The fracture dislocations with paraplegia represented but a small series of the bad prognosis and high thoracic. Recovery was anticipated in half of the lumbar and cervical injuries. The cord damage frequently occurring at time of injury very often was the result of faulty transportation. Special precautions always should be taken to avoid flexion of the spine. Patient should be lifted face downward when transportation is advisable. The nursing of these cases is facilitated by immobilization of the patient in a *plaster body jacket*. If the

spine is extended, cord pressure is controlled with far greater certainty than by laminectomy.

Sources of Failure in Treatment—

The common sources of failure in treatment were due to incomplete hyperextension of the spine by the lower table being higher than the upper one or the lower table being too far up on the thighs. Too generously cutting out the plaster defeated the purpose of immobilization by allowing the patient to resume spinal flexion. Removing the jacket too early was another source of failure. Comminuted fractures were particularly slow in uniting and the jacket should be



Fig 27—Incorrectly applied plaster cast. It is cut too high at the groins and too low over the chest. Displacement of the fracture will recur (Watson-Jones' J Bone and Joint Surg (July) 1938)

retained for 6 months. Hyperextension fractures caused the fracture of the pedicles. Fibrous union following immobilization was a little more common than bony union. This, however, was usually adequate. Lumbar spine fracture dislo-

cation took place with a locking of the articular processes. If this was hyperextended without first correcting the dislocation, cord damage was done by widening the intervertebral spaces and by putting increased stretching on the

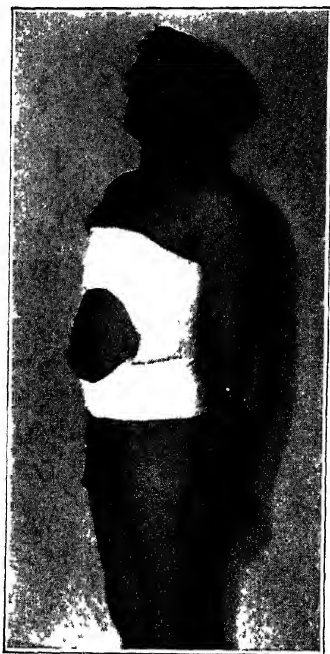


Fig 28—A plaster jacket which is a pure ornament. It is not immobilizing the spine at all (Watson-Jones J Bone and Joint Surg (July) 1938)

cord. Before hyperextending these cases it was necessary to expose the laminae and articular processes and frequently to remove the articular process before the dislocation was reduced by hyperextension. Decision that operative treatment was essential was made by lateral roentgenogram. In the upper lumbar region the processes are in the frontal plane, as in the cervical spine, and reduction might succeed with a rotary shift of the spine.

Fracture Dislocation of the Spine—Interlocked Articular Processes as a Complication—A Munro and C. G. Irwin³⁰ reported that inter-

locked articular processes complicating fracture dislocation of the spine produced by indirect violence were most common in the lumbar region with a force applied to the shoulders or upper dorsal region which forced the spine into acute flexion. The inferior articular processes were brought to rest upon the lamina of the subjacent vertebra in front of the corresponding superior process. This position usually occurred if there was an accompanying compression fracture of the vertebral body. The danger of paraplegia was from concussion, edema of cord, extravasated blood, hematomyelia, attenuation of cord or delay in reduction.



Fig 29—The patient can flex the spine almost as freely as if he were not in plaster at all (Watson-Jones J Bone and Joint Surg (July) 1938)

Treatment—The treatment as advocated by Balo was that of *manipulation* bringing the spine into flexion, then *longitudinal torsion* to either side, with a final position of hyperextension

The author, however, advocated an *open reduction* as being the safer method. Under novocain anesthesia the spinous processes and laminae were exposed, the superior facet of the subadjacent vertebra was then removed on 1 side and reduction was accomplished by hyperextension

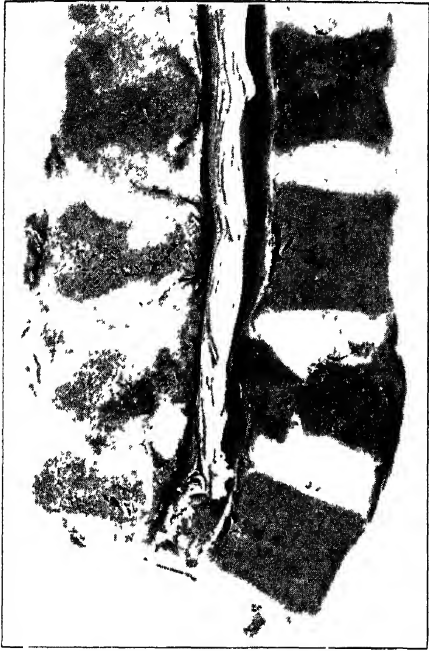


Fig 30—Case 1 Postmortem specimen (Courtesy, Journal of Bone and Joint Surgery, July, 1938)

from a pulley block attached to the patient's legs. It was occasionally necessary to remove both superior facets in order to accomplish the reduction. The postoperative care was facilitated by the use of a *plaster bed* made prior to operation with skeletal traction by means of Kirchner wires through condyles of both femora. Also used are *physiotherapy, massage* and *muscle setting exercises* with particular attention to paralytic ileus or bladder retention. When the patient had recovered from his paraplegia or if no paraplegia was present at time of operation, a *hyperextension jacket* was applied and patient became ambulatory within a few days.

Thoracic and Lumbar Vertebral Body Fracture and Dislocation—*Cord Injury During Reduction*—

W. A. Rogers³¹ found that the danger of cord injury during reduction of a fractured vertebra by hyperextension was likely in fractures involving the posterior wall of the body and in all dislocations. He stated the importance of determining the alignment of the articular processes. If the articular processes locked or would lock if the spine was extended, and if the articular processes were not in line in the anteroposterior roentgen film, open reduction was done. The laminae and articular facets were exposed posteriorly.



Fig 31—Case 1 Crush fracture involving the posterior wall of the centrum of the fourth lumbar vertebra. Mild wedge-shaped compression fracture of the centrum of the second lumbar vertebra. (Courtesy, Journal of Bone and Joint Surgery, July, 1938)

The facets were unlocked and realigned by flexing the spine and rotating it, using a periosteal elevator as a pry. Hyperextension was then applied in order to complete the reduction and a jacket applied.

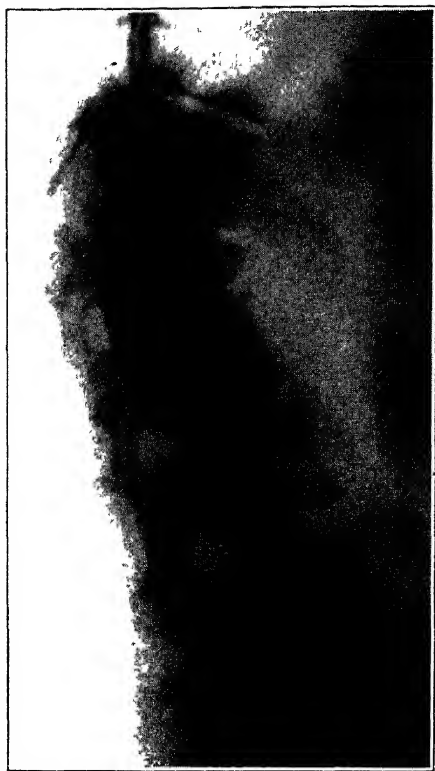


Fig 32—Case 3 Roentgenogram on admission, showing fracture dislocation of the eleventh and twelfth thoracic vertebrae (Courtesy, Journal of Bone and Joint Surgery, July, 1938)

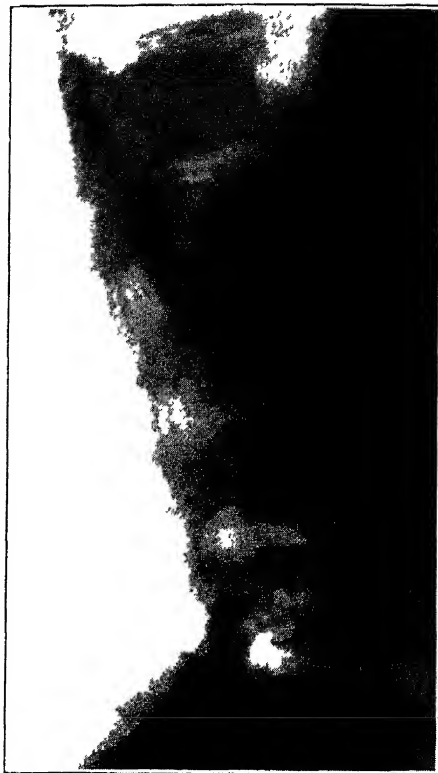


Fig 33—Case 3 Correction obtained by traction extension. The dislocation has not been reduced, posterior replacement of the eleventh thoracic vertebra has not occurred (Courtesy, Journal of Bone and Joint Surgery, July, 1938)

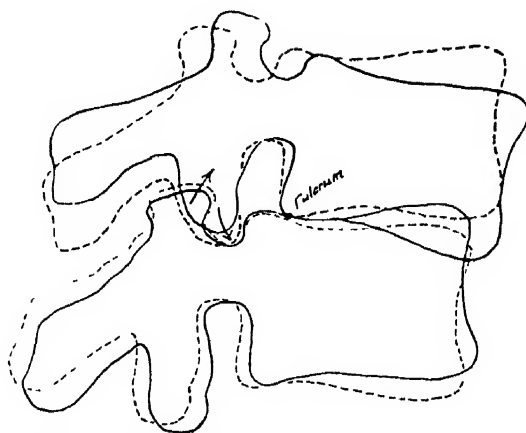


Fig 34—Diagram showing the effect of extension in fracture dislocation when the posterior articular processes do not engage normally. If the processes do not lock to prevent further extension, cord or root injury may result from the maneuver by encroachment of lamina and processes on the neural canal, as occurred in Case 3 (Courtesy, Journal of Bone and Joint Surgery, July, 1938)

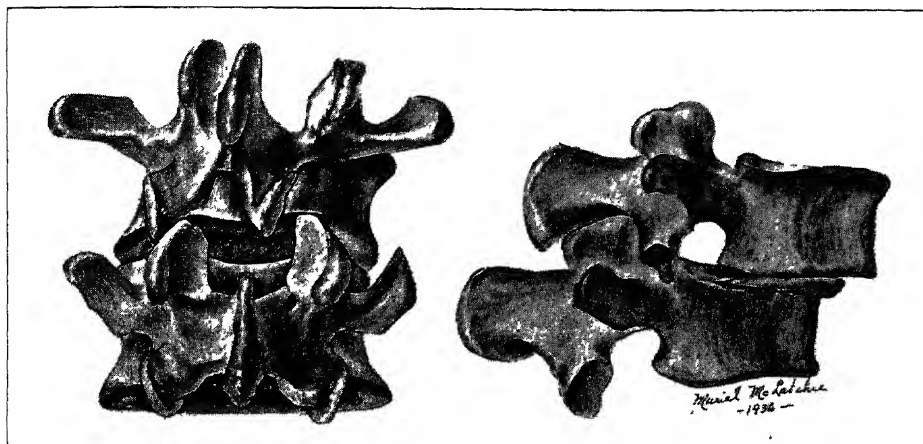


Fig 35—Case 4. Appearance of the articular processes at operation.
(Rogers J Bone and Joint Surg. (July) 1938.)

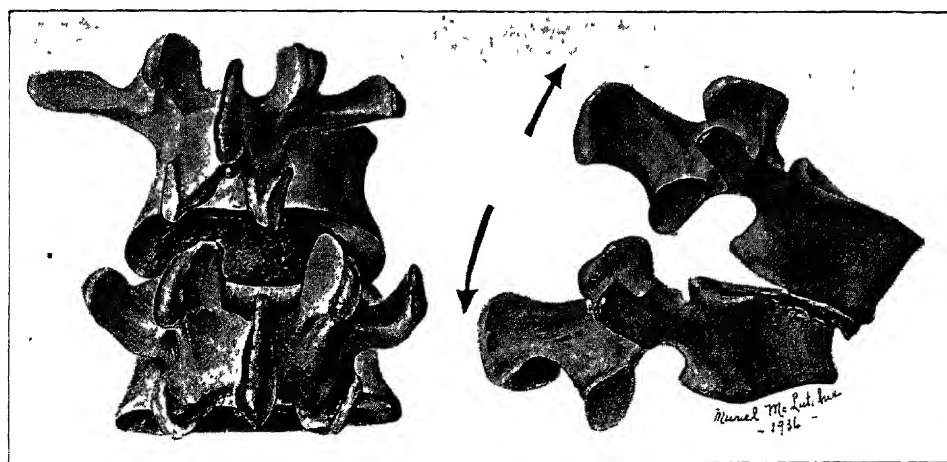
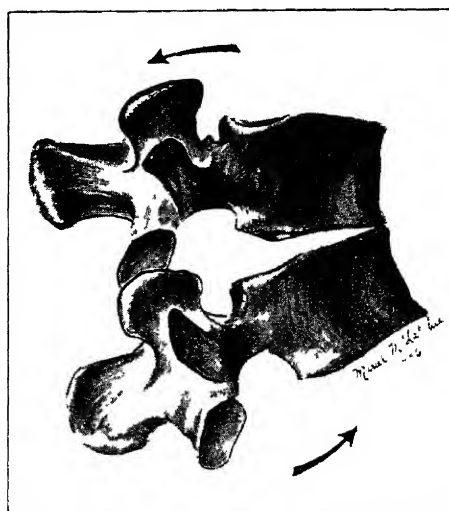
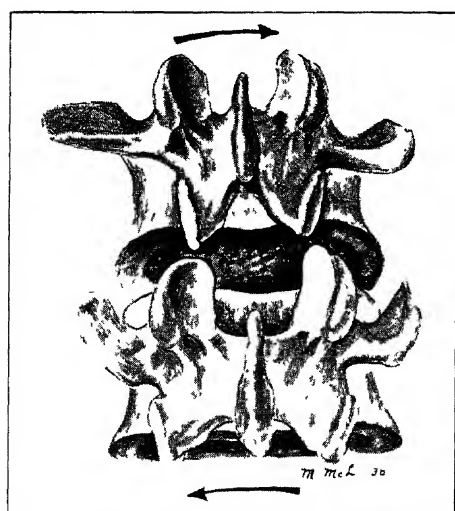


Fig 36—Case 4 Flexion aided by dissection frees the articular processes.
(Rogers J. Bone and Joint Surg. (July) 1938)



Figs 37A and 37B—Case 4 Rotation realigns the displaced articular processes
(Rogers J Bone and Joint Surg (July) 1938)

FRACTURES OF THE NECK OF THE FEMUR

Cleveland and Bosworth³² reviewed a series of 50 consecutive fractures of the neck of the femur from January 1930 to December 1934. The patients were from both wards and private floors and represented the work of 15 surgeons. The average age of patients was 64½ years

were from unrelated causes. The immediate mortality in which the injury played an important part was 14 per cent. The average age was 76 years. Of the ward cases 18 per cent died under treatment and of the private cases, 5.8 per cent. This factor indicated the importance of constant nursing care. In the evaluation of results it was pointed

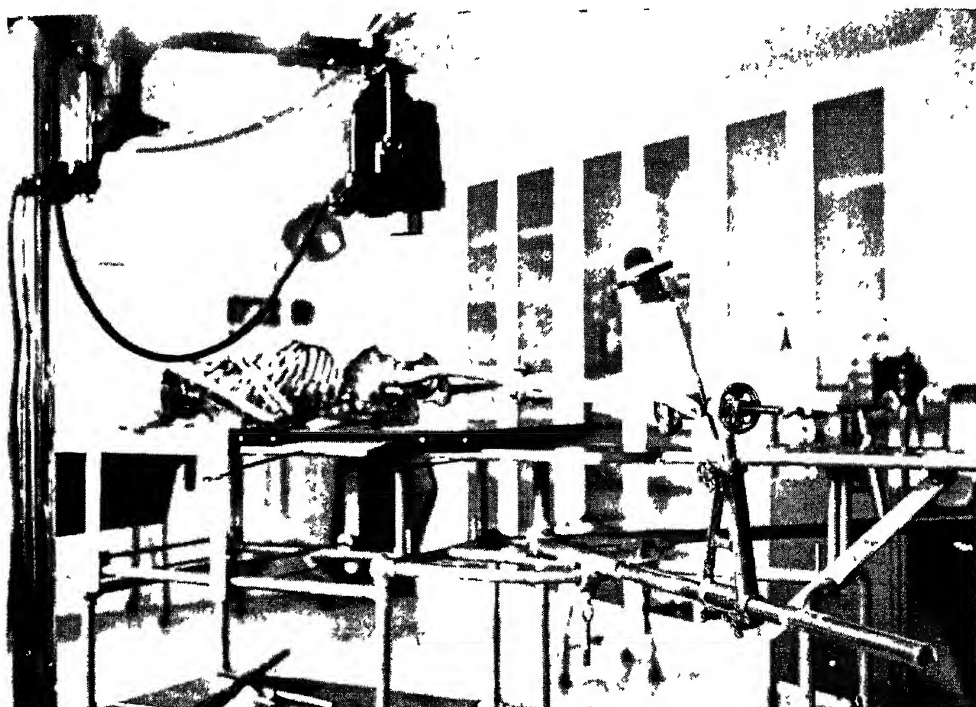


Fig. 38—Method of getting an anteroposterior view of the fracture. The fracture has been reduced and the feet have been tied to the foot pieces, so that the position of the fragments remains constant throughout the operation. (Carothers. *Annals of Surgery* (June) 1938.)

The length of hospital stay for the ward patients was an average of 122½ days, at a cost of \$671.50 each, excluding cost of x-rays, use of operating room, etc.; for the private cases 134 days and \$1,000 respectively, exclusive of nurses, x-rays, operating room and surgeons' fees. The cases were treated by conservative methods. In 40, *manipulation* was used and *immobilization* by means of *plaster of Paris spica bandage*. There was a gross mortality of 22 per cent from January 1930 to July 1936. Four deaths

were from unrelated causes. The immediate mortality in which the injury played an important part was 14 per cent. The average age was 76 years. Of the ward cases 18 per cent died under treatment and of the private cases, 5.8 per cent. This factor indicated the importance of constant nursing care. In the evaluation of results it was pointed out that union was not the only criterion. Pain, limp, limited motion and attendant disability were more important with the patient than union or nonunion. There were 19 patients in the 48 known end results who had a bony union. This was 38 per cent of the entire series, or 46.5 per cent of the 41 surviving long enough to get union. The average age of these patients with union was 59.5 years. Of the 19 patients who had united fracture, 10 had no original displacement; 8 of these had an almost perfect range of mo-

tion with little or no shortening, no limp and were rated as an excellent result. Two others were manipulated in a mistaken attempt to reduce the fracture. Though they united there were marked changes in the femoral head which lead to absorption and stiffness of the hip joint. Of the 9 other cases with union who had original displacement, only 2

motion at the hip joint and to a lesser degree at the knee joint. Of the high percentage of union in the private patients, 5 of the 9 with union had no original displacement. The factors concerned in union of fracture were taken up in the following order:

1. Method of treatment: Patients treated in plaster of Paris spica following manipula-

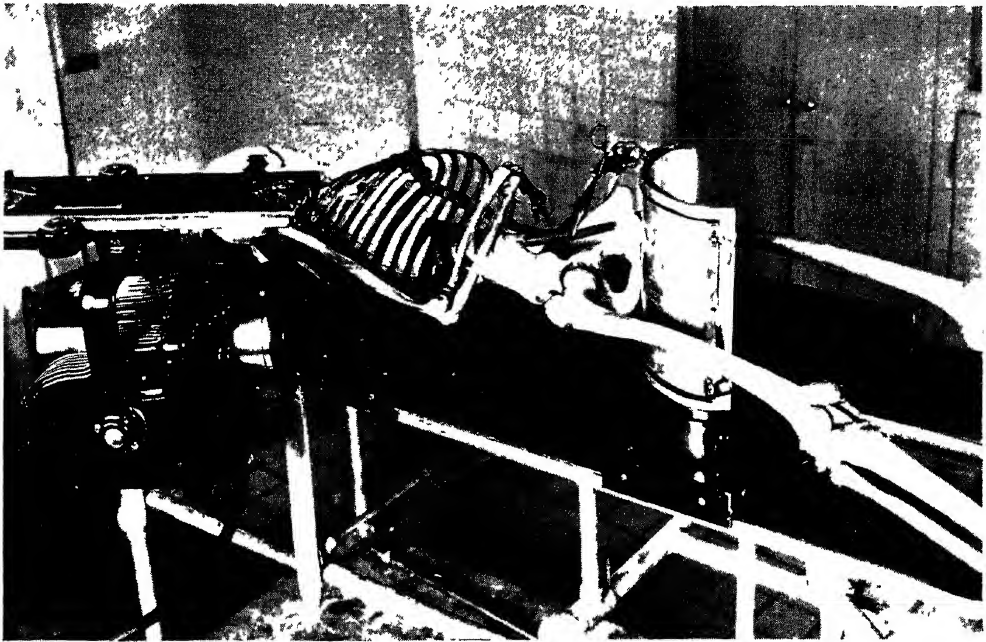


Fig 39—Method of getting a lateral view of the fracture. The curved cassette is placed upon the table firmly, which causes the lower edge of the film to be horizontal. The lateral angle of the neck as it appears at that moment, with the feet tied as they are, is easily seen on the resulting film. Note hemostat clamped to Poupart's ligament at its middle is directly over center of acetabulum (Carothers' *Annals of Surgery* (June) 1938)

had perfect functional, cosmetic and anatomical results. "The secret of an excellent union in the fracture of the neck of the femur in our series was one that showed no original displacement and was then unmolested other than to protect it when union took place." There were 20 living cases with nonunion. The average age was 68.5 years. Of these, 7 walked fairly well and were able to engage in a certain amount of normal activity. Patients with a nonunion, practically without exception, showed a limitation of

tion showed a percentage of union equal to the entire group.

Traction was the least successful and thought to have no place in the treatment of fractures of the neck of the femur.

No immobilization, other than sandbags, showed the highest percentage of union. However, these cases had no original displacement.

2. Failure to reduce the fracture must be recognized by means of anteroposterior and lateral views of the hip.

3. Rotation of the femoral head. Frequently an impingement of the fragment of the inferior anterior portion of the neck on the lower margin of the head caused an upward and anterior

rotation as the thigh became adducted, externally rotated and displaced upward. This rotation prevented satisfactory abduction of the thigh to obtain reduction, abnormal amount of blood clot formed between the fragment ends,

4. Fractures that suffered from overtreatment, such as too wide abduction and too much internal rotation.

5. Incorrect interpretation of roentgenograms

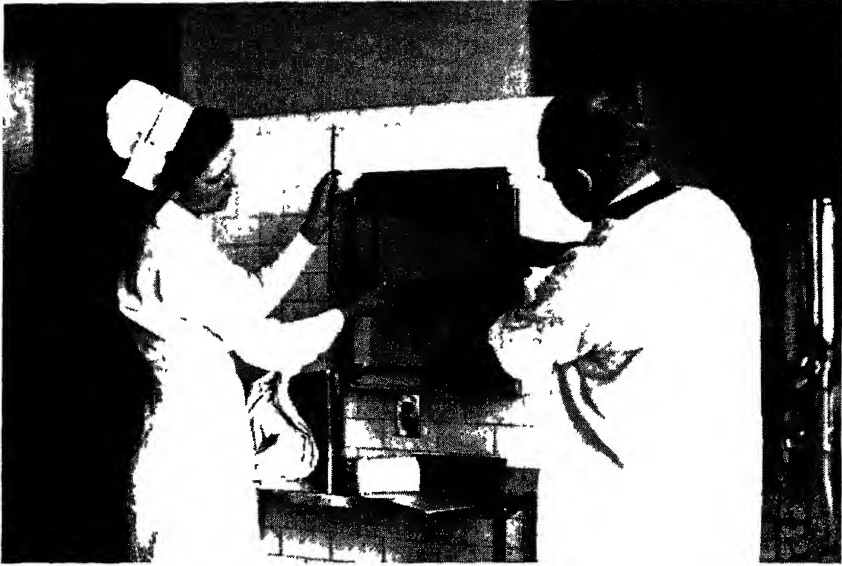


Fig 40—With one edge of the card held parallel to the lower edge of the film, the other edge of the card can be cut to show the angle of the neck (Carothers Annals of Surgery (June) 1938)

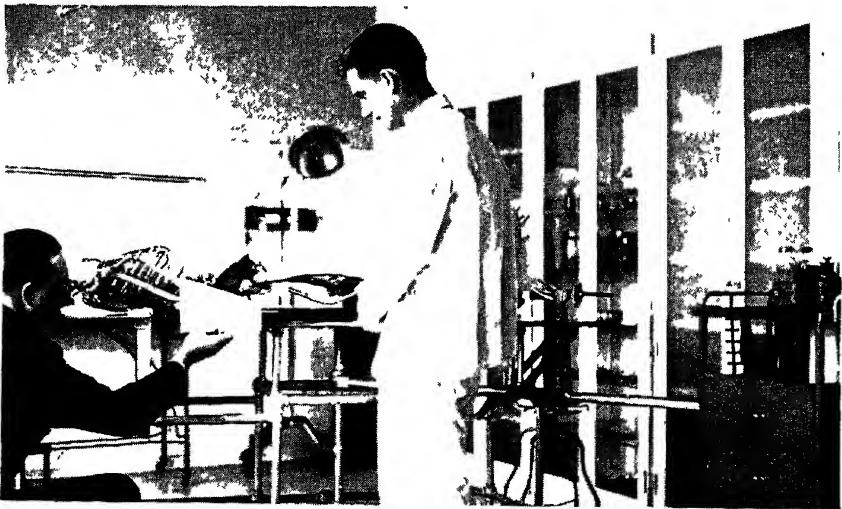


Fig 41—This card is held by an assistant who can line up the pin in the proper direction with his eye (Carothers Annals of Surgery (June) 1938)

and the anatomical position of the head on the neck was impossible to secure. Holding apart the fracture surfaces by spiculations decreased the vascular supply. If rotation was found, open reduction was advisable. Percussion impaction of mismatched spicules was illogical

6. Death of femoral head.

7. Unreadable roentgenograms

R. G. Carothers³³ presented a simplified technic for directing the insertion of pins or Smith-Peterson nail for fixation

of femoral neck fractures after reduction. The patient was placed on a Hawley table with a wooden frame under the fractured hip. The wooden frame was just large enough to permit the insertion of an x-ray cassette.

Following reduction of the hip the legs of the subject were held by bandaging the feet to the foot stirrups (Fig. 38). An anteroposterior x-ray film was taken

were then inserted from just below the trochanter toward the middle of Poupert's ligament at an anteroposterior angle determined by the cardboard pattern.

Importance of Restoration of Blood Supply—F. H. Albee³⁴ stressed the importance of re-establishment of circulation to the fracture head. According to Wolcott the ligamentum teres in 15 per cent of the cases had no vessels of suffi-



Fig 42—An Allis forceps has been placed at the middle of Poupert's ligament. Looking at the patient from above, it will be seen that it is situated directly over the center of the acetabulum, and that a pin directed toward this point will go into the head. (Carothers. *Annals of Surgery* (June) 1938.)

and by means of a curved cassette a lateral film was obtained (Fig 39). As the lower margin of the latter film was parallel to the table surface, a piece of cardboard could be shaped to give the angle of femoral neck in relation to the table surface (Fig 40). This cardboard was used to direct the nail in its anteroposterior course (Fig 41). A towel clip was placed in the middle of Poupert's ligament (Fig 42). This point lay directly over the center of the acetabulum, but could readily be verified by an anteroposterior x-ray film. The pins or nail

of sufficient size to allow injection of mercury. In 413 hip reconstruction operations, Albee has never found bleeding from the cut ligamentum teres. In many cases of fracture the ligamentum teres was torn. An autogenous bone graft permitted an ingrowth of vascular channels from the great trochanter. In a few cases when impaction had not been obtained, the graft bridging the gap between the fragments, even in the presence of surrounding joint fluid, had hypertrophied to become indistinguishable from the normal neck.

Treatment by Oblique Osteotomy—T. P. McMurray³⁵ advocated an *oblique osteotomy* as certain method of obtaining union of a transcervical fracture of the femur. First the shortening and ex-

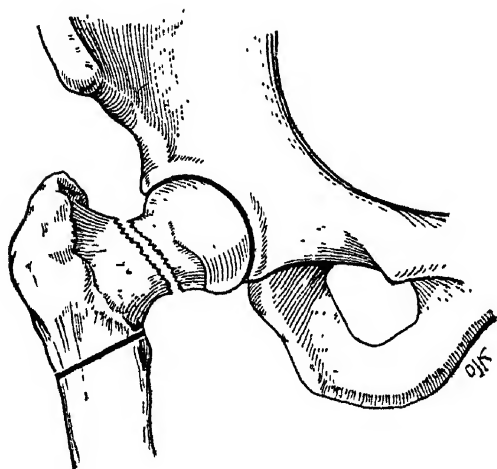


Fig. 43—Fracture of the neck of the femur, showing line of osteotomy. (Courtesy, British Medical Journal, Feb. 12, 1938.)

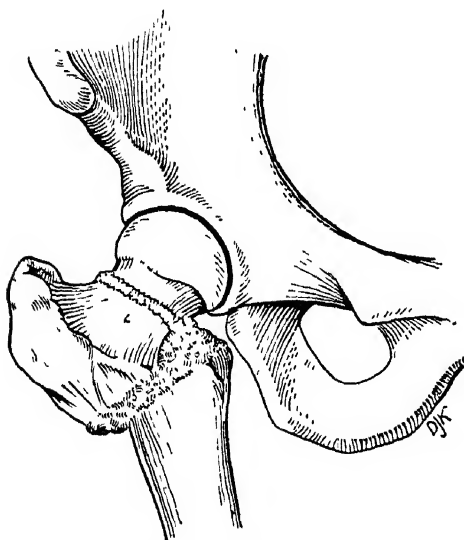


Fig. 44—After displacement inwards of the shaft of the femur, showing the tilting of the head and of the trochanteric fragment (Courtesy, British Medical Journal, Feb. 12, 1938.)

ternal rotation of the extremity are correction, then through a longitudinal incision over the femoral trochanter, the lower level of the fractured femoral neck

is determined and at this point an oblique osteotomy was done. The femoral shaft was displaced mesially so as to engage beneath the femoral neck and lower border of the cotyloid ligament. Fixation was maintained for a period of $3\frac{1}{2}$ months by means of a plaster bandage from toes to lower ribs. After 8 weeks the foot and ankle were freed for exercises. Twenty-seven cases of non-union and 4 recent fractures of the neck of the femur were treated successfully by this method. The only disadvantages were minor ones, a $\frac{1}{2}$ inch to $\frac{3}{4}$ inch shortening of the extremity and an inability to adduct the leg past the midline of the extremity.

Central Fracture of the Neck of the Femur

J. S. Speed³⁶ reviewed the central fractures of the neck of the femur treated at the Willis C. Campbell Clinic. In 1934 the cases treated by the Whitman method exclusive of incomplete or impacted fractures showed a 53.3 per cent solid bony union. The mortality was 12 per cent. There were 34.7 per cent living with nonunion. The causes for the latter were improper or incomplete reduction with failure of accurate apposition of fractured surfaces or interposed capsular tissue, insufficient immobilization which was particularly true in obese subjects; and disturbance in the circulation of the head and neck of the femur. The latter was from the ligamentum teres which became less or absent as age advanced, the nutrient artery and its branches coming in through the cancellous portion of the neck, and the capsular arteries. In a fracture, almost the entire blood supply to the head was severed. Roentgenologic and histologic studies of femoral heads removed during hip reconstruction operations from cases in the above series resulted as follows:

Solid bony union with viable head . . .	48%
Solid bony union with necrotic head . . .	4%
Nonunion with viable head	17%
Nonunion with necrotic head	31%

Of 44 cases treated by internal fixation with the Smith-Petersen nail but 21 had been observed long enough after removal of the nail for analysis.

Solid bony union with viable head . . .	16 (79%)
Solid bony union with necrotic head . . .	2 (9%)
Nonunion	3 (12%)

Fresh Fracture of the Os Calcis³⁷

This is an excellent review of the literature on fractures of the os calcis as well as a well-written report of 8 cases of such fracture treated by immediate reduction with gas-oxygen anesthesia and a modified carpenter's clamp used. Fig. 45 shows the clamp used in molding the fragments and reducing the fracture. Fig. 46 shows the first position of application of force, with two hemi-

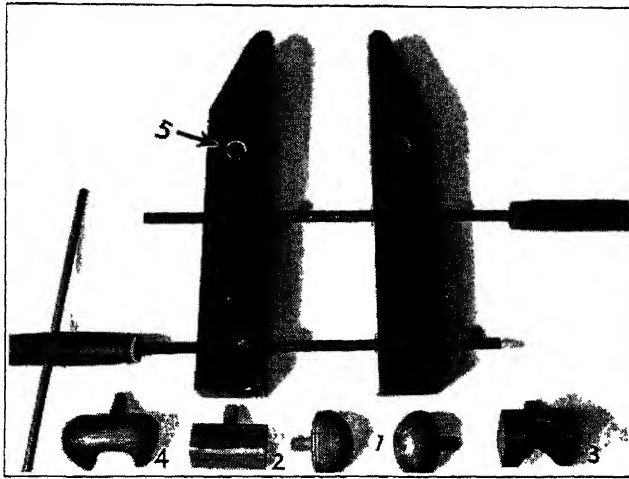


Fig. 45—Clamp used in molding the fragments and reducing the fracture. 1, hemispherical blocks for lateral modeling, 2, oblong block used against plantar surface, 3, grooved block to fit around the attachment of the Achilles tendon over the tuberosity, 4, semilunar block used beneath the lateral malleolus, and 5, holes through the jaws to carry muslin ties to hold the clamp to the foot (Courtesy, Arch Surg (May) 1938)

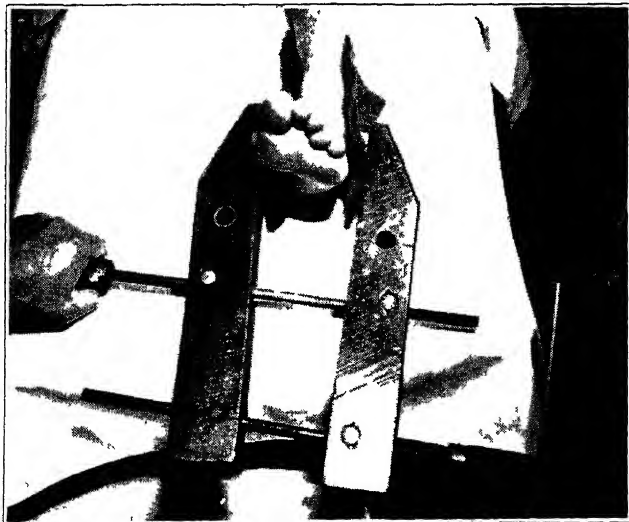


Fig. 46—First position of application of force, with two hemispherical blocks, or jaws (Courtesy, Arch Surg (May) 1938)



Fig 47—Second position, in which one hemispherical block and the semilunar block compress the fragment beneath the lateral malleolus that might extrude (Courtesy, Arch Surg (May) 1938)

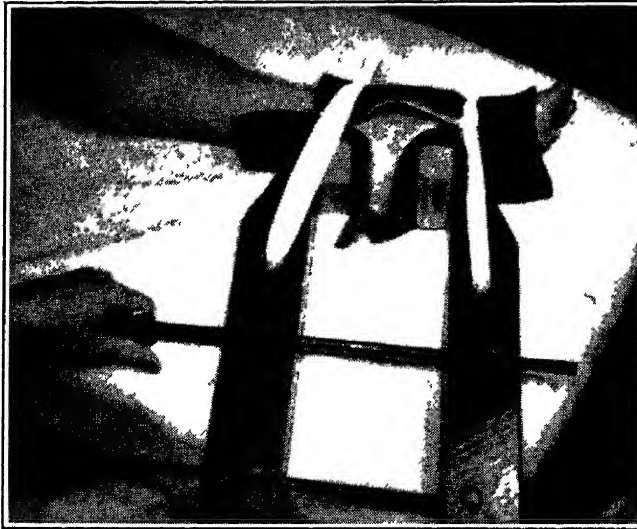


Fig 48—Third position, in which blocks 2 and 3 are used to bring down the posterior tuberosity and raise the head of the os calcis. The clamp cannot get away from the foot because of the muslin ties (Courtesy, Arch Surg (May) 1938)



Fig 49—Note the incision over the great trochanter from which spongiosa or cancellous bone was obtained (Medical Journal of Australia)

spherical blocks or jaws, and Fig. 47 shows the second position in which the hemispherical block and the semilunar block compress the fragment beneath the lateral malleolus that might extrude. Fig. 48 shows how the blocks bring down the posterior tuberosity and raise the head of the os calcis. Of the 8 patients treated by this closed method of reduction, 6 made a comparatively rapid recovery. One had posttraumatic arthritis in

multiple drill holes crossing the site of fracture from the bone ends was preferred. The Matti procedure consisted first of removing a button of bone from the greater trochanter of the femur. Then with a curette several dessertspoonfuls of spongiosa were removed, the button of bone was repositioned in the cortex of the trochanter and the wound closed. The site of nonunion was then exposed by an incision through the skin down to

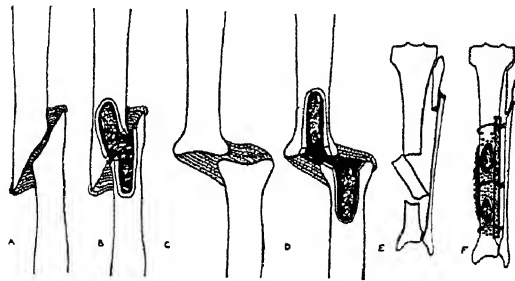


Fig 50—Diagrams indicating methods of dealing with various displacements A—Ununited oblique fracture with lateral displacement B—A deep and broad gutter has been cut in both fragments which now communicate by their medullary cavities Lateral displacement is ignored. C—Pseudarthrosis in a transverse laterally displaced fracture D—Without interference with the displacement a communicating gutter across the pseudarthrosis is cut in both bones. E—Comminuted fracture of tibia (ununited) F—The comminuted fragment was replaced, guttered at both ends so that there it communicated with medullary cavities of both ends of the tibia and packed with spongiosa paste Numerous drill holes in the fragments Thick lay-on tibial transplant with a half-inch layer of cancellous bone clinging to cortical part of graft. Oblique fibula osteotomy to correct shortening In most cases with a transverse or oblique fracture of the tibia the fibula, even if ununited, can be ignored (Medical Journal of Australia)

the subaloid joint, refused arthrodesis and was given a 50 per cent disability allowance The other patient disappeared before treatment had been completed The author advocates this method of treatment because it is simple, effective, comfortable for the patient and physiologically reasonable and removes the necessity for tenotomy

Ununited Fractures

Treatment—Matti's spongiosa bone transplant for ununited fractures was reviewed by T King.³⁸ This was particularly adaptable to fractures of the femur, humerus, radius and those of the tibia with poor alignment of the fragments In tibial fractures with good alignment mul-

bone The fibrotic tissue and periosteum were reflected except on one side. The latter was maintained particularly to give some fixation of the fracture ends

The ends of the fragments were then freshened with a saw or osteotome and the segment of the cortex was removed from the accessible surface on either side of the fracture line With a curette the medullary cavity was reestablished over the fracture site for several inches in either fragment or until bleeding cancellous bone was reached The spongiosa which had been removed from the trochanter was then placed in a prepared cavity and pressed down with the handle of an osteotome so that it formed a paste on the sides of the new medullary cavity.

Cortical bone that had been removed from the fracture site was ground into small fragments and replaced across the fracture line. The periosteal ligaments were closed. No cast was applied for fixation. The leg was left on a splint for 10 days, then alignment of the fragments

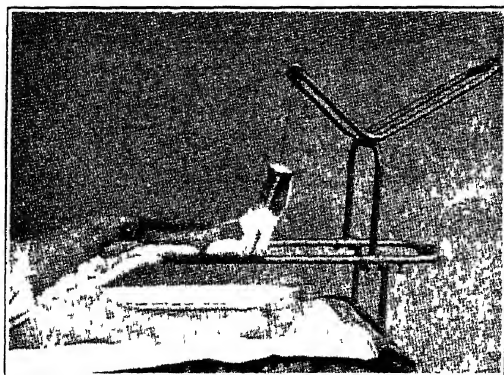


Fig 51—After operations on the lower extremity the limb is suspended in a Braun splint. After operations on the tibia, encasement in a plaster cast under 7 to 14 days is dangerous even if padded. The case illustrated is a simple fracture of the tibia and fibula. Had a plaster cast been applied, it would have been blamed for the "fracture blisters" and swelling (Medical Journal of Australia)

was corrected and a plaster cast applied for fixation.

In those cases with fracture of the shaft in which there was poor alignment or 2 ununited fractures with a central fragment, a full thickness tibial graft one-half the length of the fractured bone supplemented the spongiosa grafting which was done at either end of the fragment. The incision was not extended the length of the graft, but its insertion was attained by tunneling its ends beneath the muscles on either side. Rustless steel V-2A wire was used to hold the graft approximated to the shaft and fragment. The author reported that when infection occurred cortical chips were discharged from the wound as sequestra but union was not delayed. He stressed the impor-

tance of working without tourniquet in order to determine the amount of resection of cortical and medullary bone necessary to attain good circulation.

The Healing of Fractures of Atrophic Bones

J. Goisman and E. L. Compere³⁹ found that in increased vitamin D in the diet did not influence the healing time in atrophic bones or normal bones of young rats. There was evidence to indicate that massive doses of calcium or vitamin D might produce an inhibiting effect causing delayed union.

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RADIOLOGY, X-RAYS, X-RAY DIAGNOSIS

By ROBERT SHOEMAKER, 3RD, M.D

ROENTGEN VISUALIZATION AND DIAGNOSIS OF BREAST LESIONS BY MEANS OF CONTRAST MEDIA¹

During the past 2 years the authors have developed a method of diagnosing the various types of mammary neoplasms roentgenologically by means of contrast media. They have done this by 2 methods. In the first method the milk ducts are injected with some radiopaque substances and then stereoscopic films are made. The "mammograms" present accurate anatomical patterns of the injected ducts. Any pathological condition which alters their size, shape or conformation is readily detected. In the second method, termed "aeromammography," CO₂ is injected into the retro-mammary and premammary spaces in such a manner that the diffusing gas forms a contrast capsule around the parenchymal tissue and reveals any neoplasms contained therein.

Technic of Opaque Injection—Thorotrast, a 25 per cent colloidal solution of thorium dioxide, has been found more satisfactory than other radiopaque

solutions for injection into the lactiferous ducts. The breast is thoroughly cleansed as for any surgical procedure and only sterile instruments and solutions are used. Hot moist compresses are applied to each nipple for at least 15 minutes. The moisture softens any plugs of inspissated material which may be occluding the ducts and the heat relaxes their sphincters. A gentle stripping massage of the nipple will then express a few drops of secretion to establish the orifices of the milk ducts. These are cannulized with a specially constructed needle (Fig 1). If properly inserted the cannula will slide back and forth in the duct for a distance of 1 cm. without causing pain, but if it pierces the duct wall, the slightest manipulation becomes very annoying. In breasts that have never lactated, breasts with inverted nipples and in very obese breasts, it is sometimes difficult to locate the orifices of the ducts. No attempt should be made to cannulize ducts which are not patent since forcing the contrast solution into a collapsed duct invariably results in periductal extravasation. Only

slight pressure is required to introduce from 0.5 cc. to 2 cc. of the contrast solution into each duct. Usually the entire breast can be visualized by injecting 6 to 8 of the larger ducts.



Fig 1—Cannulization of the milk ducts with a No. 27 Hicken breast cannula (Am J Roentgenol, March, 1938)

In cases of tumor it is best to inject the ducts leading to the tumor region first and to make films of these ducts and so avoid superimposition of shadows of the other ducts.

After stereoscopic films have been made, the contrast solution is removed from the ducts with a breast pump, supplemented by milking massage of the nipple. At times a gentle saline lavage of the ducts will expedite their evacuation.

Technic of Gas Injection—The authors have found CO_2 better than oxygen or air for injection into the premammary and retromammary tissues. The apparatus which they use consists of a small tank of CO_2 , reducing valve,

rubber tubing, flask of sterile water, and another piece of rubber tubing connecting with a 20-gauge needle. This apparatus is shown in Fig. 2. When the CO_2 is introduced into the retromammary tissues it separates the breast from its muscular bed, elevating it from the chest wall. Then the needle is withdrawn and reinserted into the premammary subcutaneous tissues. The CO_2 separates the skin from the underlying matrix. The true mammary tissues are thus surrounded by a contrast capsule of gas which greatly enhances their visualization, as shown in Fig. 3. If correctly inflated, the breast should be 2 or 3 times larger than its uninjected mate. It is imperative that the stereoscopic

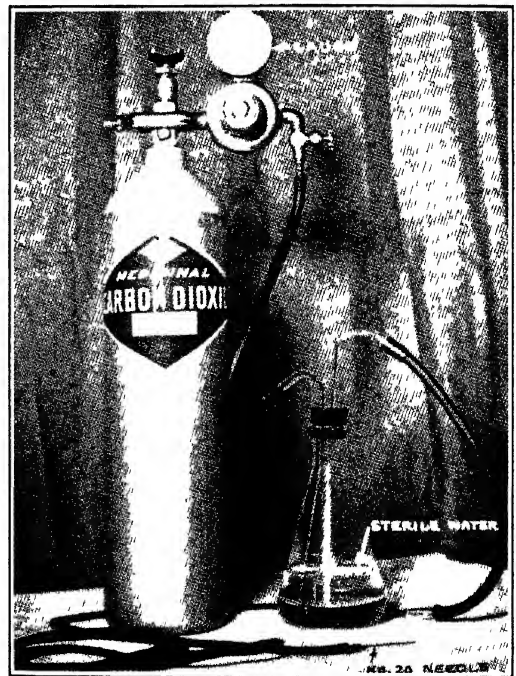


Fig 2—Apparatus devised for CO_2 insufflations of the breast (Am J Roentgenol, March, 1938)

roentgenograms be taken immediately, for a delay or 2 or 3 minutes is sufficient to permit a partial absorption of CO_2 which results in unsatisfactory mammograms.

Roentgenographic Technic—The patient is placed in a lateral recumbent position with the injected breast supported by a 17 or 23 degree angle board as shown in Fig. 4. The arm on the affected side is held in abduction and the other hand retracts the upper breast away from the roentgenographic field. The film is placed so as to include the

and smaller lacteals are situated deep within the stroma, the latter converging to form the large ampulla which opens on the surface of the nipple (Fig. 5). The 4 zones which should be visualized by x-ray films are: (1) Skin, (2) translucent premammary tissue, (3) dense matrix with its characteristic striations, (4) retromammary tissue.

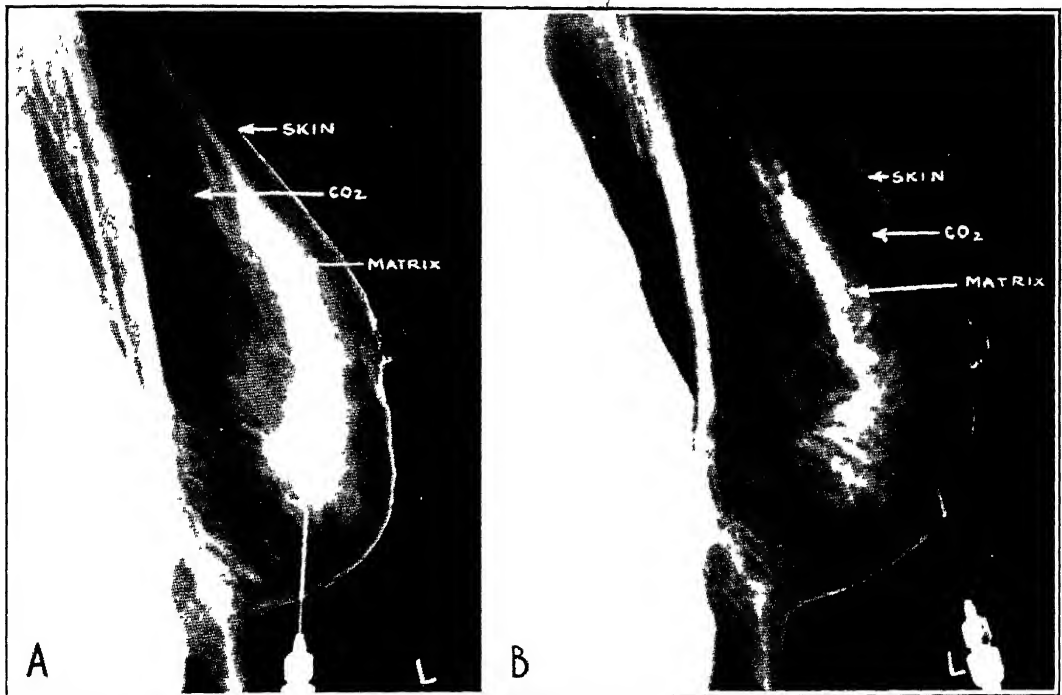


Fig 3 The retromammary, *A*, and the premammary, *B*, spaces are inflated with CO₂ until the gas completely surrounds the matrix tissue (Am J Roentgenol, March, 1938)

entire mammary gland and the axilla. Cardboard holders give better soft tissue details than do screens, except in unusually large breasts. All roentgenograms are taken at a distance of 75 cm., 45 to 60 kv., 45 to 50 ma., 1 to 3 seconds.

Interpretation—Normal—A normal well-developed mammary gland consists of 15 to 20 pyramidal lobules containing secreting glands, collecting tubules and matrix tissue. The base of each pyramid rests on the pectoral muscles and the apex points toward the nipple. The acini

Virginal Breast—In the virginal breast, active function has not developed the acinar and ductal tissues. The lobules are small, the striations appear as thin indistinct lines, the matrix tissue is irregular, mottled and semiopaque, and there is usually a large amount of adipose tissue in the premammary and retromammary spaces. If the ducts are distended with contrast material they appear as fine white threads which penetrate the matrix and form a dense network of ramifying tabules (Fig. 5). The ampullae are not dilated and the acini

are not visible for these structures do not become fully developed until lactation occurs. The uniform manner in which the ducts ramify in the stroma denies the possibility of neoplastic dis-



Fig 4—The lateral recumbent position and the use of an angle board give undistorted roentgenograms of the breast (Am J Roentgenol, March, 1938.)

tortion In the aeromammogram, the outline of the matrix is intensified by the contrast with the surrounding CO₂ (Fig 6).

Lactating Breasts—There is considerable variation in the appearance of lactating breasts depending on their size, the number of lactations experienced and the amount of milk which they produce. Active function produces a definite hypertrophy and hyperplasia of the secretory and ductal system. The striations are much larger, the amount of adipose tissue is relatively reduced and the glandular structures become more dense. The ducts are larger, they are more

numerous, their ampullae are widely dilated and the acini appear as tiny tufts or caps on the ends of the terminal lacteals (Fig. 7). The CO₂ insufflation demonstrates a marked hyperplasia of the matrix tissue and rarefied fatty tissue areas can be seen on all sides of the larger ducts.

Multiparous Breast—The multiparous breast has definite characteristics. The ductal and fibrous tissue striae are usually broader and more distinct than in the virginal and primiparous gland. The stroma appears more dense and

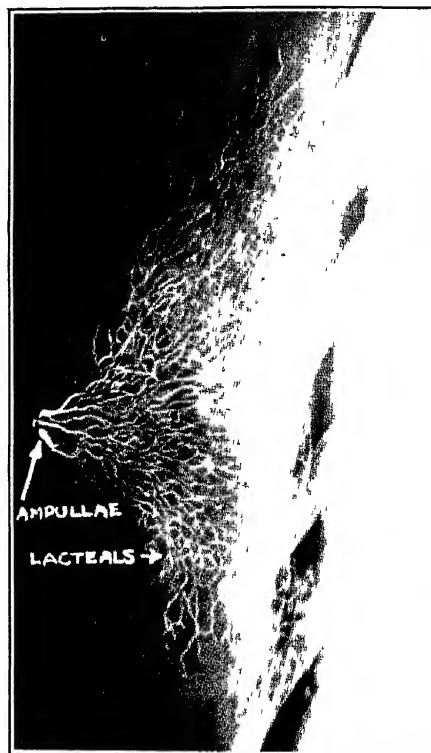


Fig 5—Virginal breast. A retouched mammogram showing the ramifying lacteals. The ducts are small, the ampullae are not dilated and the acini are not developed (Am J Roentgenol, March, 1938.)

there is less adipose tissue. The subareolar ducts are distinctly visible. In the mammograms, the ducts appear dilated, the ampullae are particularly large and the matrix consists of a network of

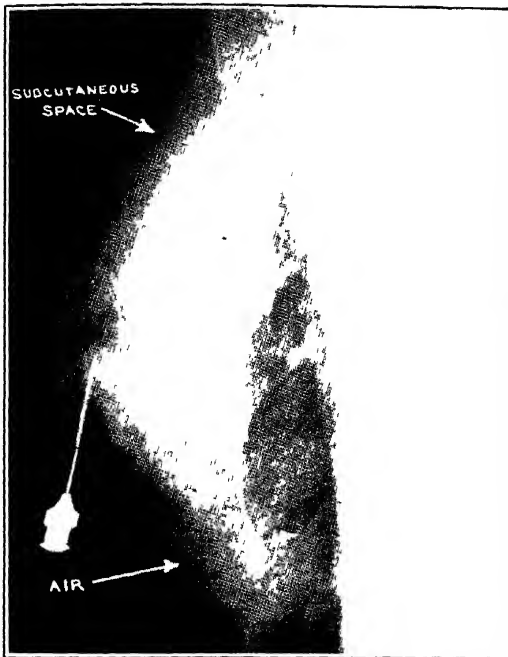


Fig. 6—CO₂ insufflations enhance the visualization of the matrix. The striations of the virginal breast are very fine (Am J Roentgenol, March, 1938)

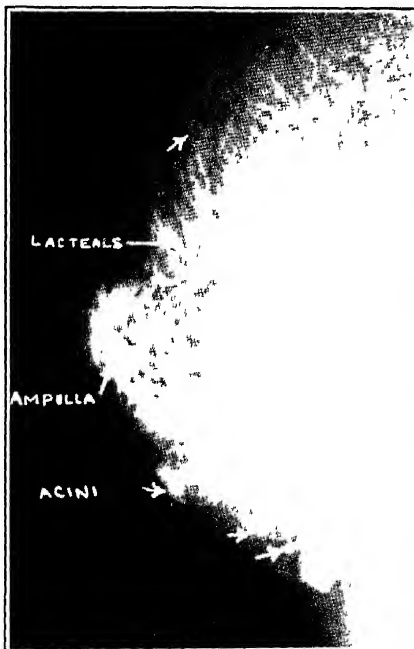


Fig. 7—Lactating breast. Manumogram on third postpartum day shows hypertrophied ducts, dilated ampullae, and fuzzy caps (acini) on the ends of the terminal lacteals (Am J Roentgenol, March, 1938)

branching lacteals. The acini are not visible in the quiescent breast, which differentiates it from the lactating organ (Fig. 8). In those mammary glands which have produced large quantities of milk, the ducts are larger than in the poorly secreting breast (Fig. 9).

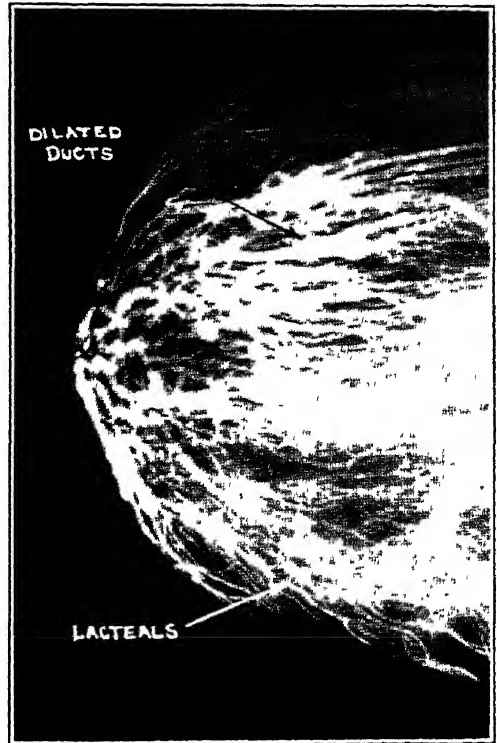


Fig. 8—Ducts of multiparous breast were injected with lipiodine. The large dilated ducts and the dense network of large lacteals indicate a "good milk producer" (Am J Roentgenol, March, 1938)

Disease produces characteristic changes in the breast pattern by displacing, obstructing, invading or destroying the lactiferous ducts. The ability to visualize such deformities is the basis of mammographic diagnosis.

Papilloma—Patients who complain of a bloody discharge from the nipple present a tantalizing diagnostic problem. The bleeding duct is cannulized and injected with thorotrast. Stereoscopic films made immediately afterwards show fill-

ing defects caused by the protrusion of the papilliferous growths into the larger ducts as shown in Fig. 10. They usually occur singly and are located in the ampulic segment of the subareolar ducts.

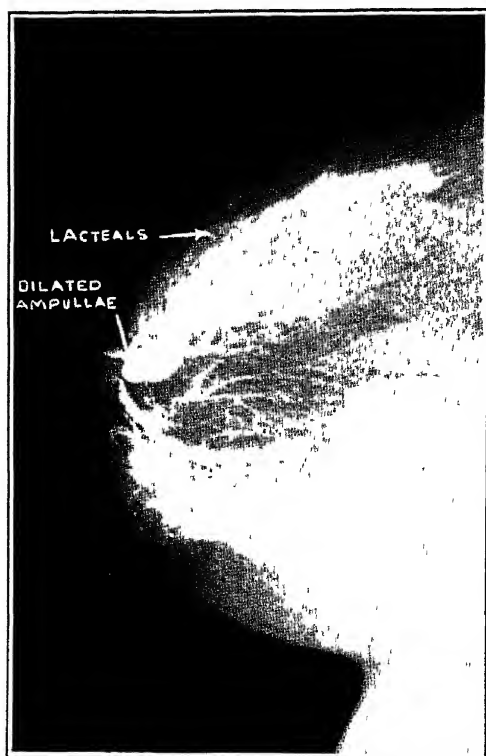


Fig 9—Multiparous breast injected with thorotrast. The small lacteals indicate a poorly functioning gland. No disturbance in the normal distribution of the ducts. (Am J Roentgenol, March, 1938.)

Occasionally they may be multiple or bilateral and for this reason the authors always study both breasts.

Cystic Disease of the Breast—

Cysts may represent a simple physiological change, as in mazoplasia, or a benign degenerative transition as chronic desquamative epithelial hyperplasia. They may develop as retention cysts, thus forming galactoceles and simple blue dome cysts, or they may occur as a degenerative phase of a rapidly growing carcinoma, sarcoma or papilloma. To consider all cysts as potentially malignant

leads to many unnecessary radical operations, but to clothe them with the mantle of benignancy and adhere to the policy of watchful waiting is often disastrous.

Infected Cyst—Localized desquamation may occur so rapidly in certain parts of the milk ducts as to form definite cysts. These cavities communicate with the duct and hence evacuate their seropurulent content through the ductal orifice. At times the cyst becomes distended and the patient complains of a palpable tumor. It may discharge completely and then defies detection. The so-called "phantom tumors" sorely vex

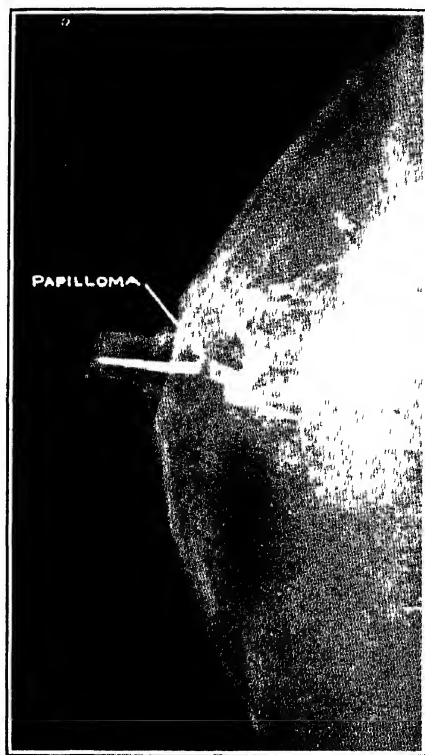


Fig 10—Retouched mammogram showing the "filling defect" caused by a non-palpable, bleeding, intraductal papilloma. (Am J Roentgenol, March, 1938.)

the physician for he is usually unable to find the "lump" which has disturbed his patient. If thorotrast is injected into the duct it may enter the cyst making it readily palpable and visualized on

x-ray films as shown in Fig. 11, 12 and 13.

Retention Cysts—Sequestered cysts which have lost their continuity with the regional lacteals frequently become distended with serous secretion and desquamative products. They are usually situated in the midmammary tissues and

can be obtained by aspirating the fluid and replacing it with air or thorotrast (Fig. 14C). If there are any papilliferous projections into the lumen of the cyst or if it communicates with other cysts or the neighboring ducts, these details will be clearly demonstrated (Fig. 14D and E).

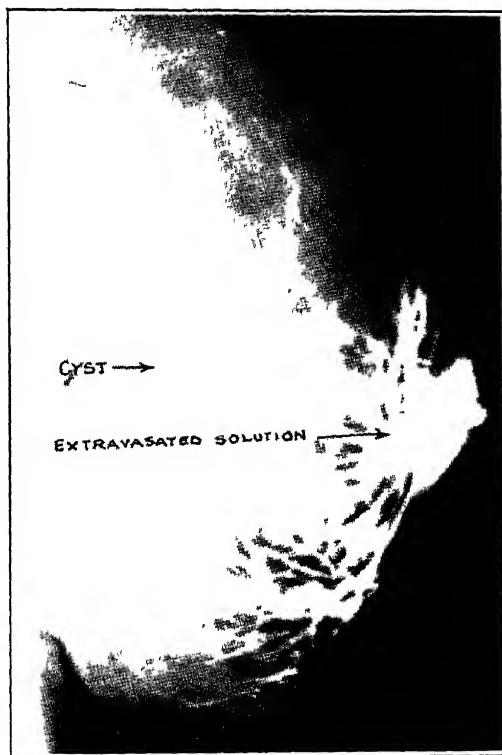


Fig. 11—A collapsed midmammary cyst was visualized by distending its discharging duct with thorotrast. Note the extravasation of the solution due to faulty technic (Am J Roentgenol, March, 1938.)

are semifluctuant, discrete and movable. They transmit light with great facility and hence appear as rarefied areas. As a rule, the roentgenographic outline of the larger cysts is very indefinite and the smaller cysts are not pictured (Fig. 14A). If the regional ducts are injected with thorotrast the mammograms reveal them to be displaced by the expanding cyst because they do not have a patent communication with it (Fig. 14B). An excellent picture of the cystic cavity

Galactoceles—These are simple retention cysts which develop in lactating breasts, and differentiation from adenoma, fibroadenoma, lipoma and carcinoma is most difficult. A tightly distended galactocele imparts a feeling of hardness akin to that of a solid tumor and the viscid secretion may absorb so much light that a definite shadow is cast on transillumination. Being retention cysts, these tumors are not reduced in size by compression. One hesitates

to perform a biopsy as division of the functioning lacteals may result in a seeping fistula

The true nature of the neoplasm can be easily determined by aspirating its

flow. This happens most commonly in virginal breasts which are not good subjects for thorotrast injections.

CO₂ insufflations, in the vast majority of cases, will intensify the outline of the parenchymal tissue and furnish enough evidence to dispel the fear of cancer. On 5 occasions the authors have found the so-called "idiopathic mastalgia" was due to real cystic degeneration of the breast.

Lipoma: Localized deposits of adipose tissue frequently occur in obese breasts. If situated in the subcutaneous area, they are readily identified as soft, encapsulated, movable, translucent

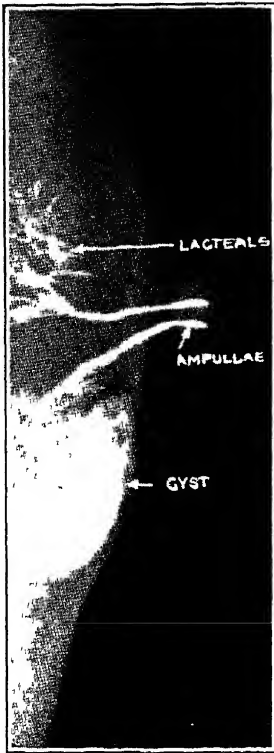


Fig 12—A collapsed cyst became visible and palpable by introducing thorotrast into some of the discharging ducts. The upper segment is that of an involuted breast (Am J Roentgenol, March, 1938)

cystic content, which should be composed of thick milk and desquamative products. The interior of the cyst can be studied by inflating it with air. If its walls are smooth and if there is no evidence of papilliferous extension into its cavity, the diagnosis of a benign galactocele is apparent.

Mazoplasia—Because of its hormonal regulation, the breast has alternating periods of hyperplasia and regression. In some instances these processes are not well regulated and the patient develops mastalgia just before each menstrual

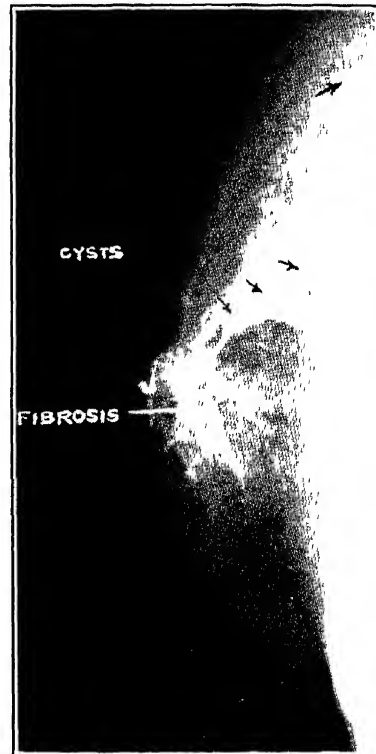


Fig 13—Multiple cystic degeneration of the milk ducts visualized by means of thorotrast (Am J Roentgenol, March, 1938)

masses. If situated in the matrix or retromammary space, differentiation is indeed difficult. Because the breasts are large, transillumination usually is not informative. Soft tissue roentgenograms

usually show the lipomatous tumor as a compact radiolucent mass, displacing the breast matrix, while other benign neoplasms have a greater radiopacity. Mammography is of no avail because the fatty infiltration of the matrix produces

same radiolucency as the adipose tissue (Fig. 15).

Fibroadenoma—These are perhaps the most commonly encountered benign solid tumors of the mammary gland. While they appear as indefinite opaque

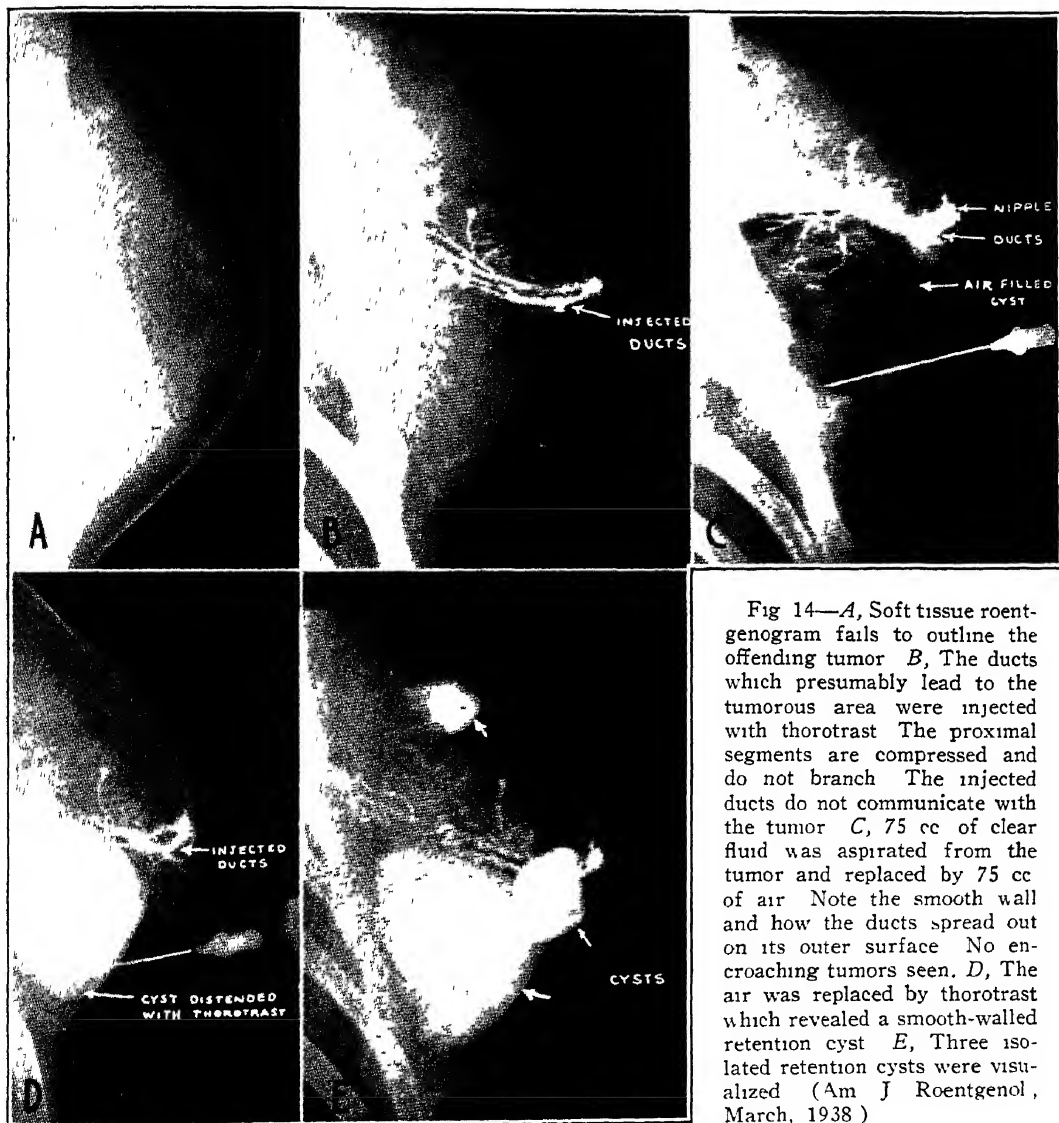


Fig 14—A, Soft tissue roentgenogram fails to outline the offending tumor B, The ducts which presumably lead to the tumorous area were injected with thorotrast. The proximal segments are compressed and do not branch. The injected ducts do not communicate with the tumor C, 75 cc of clear fluid was aspirated from the tumor and replaced by 75 cc of air. Note the smooth wall and how the ducts spread out on its outer surface. No encroaching tumors seen. D, The air was replaced by thorotrast which revealed a smooth-walled retention cyst. E, Three isolated retention cysts were visualized. (Am J Roentgenol, March, 1938.)

a pressure occlusion of the ducts and the contrast medium cannot be introduced. Properly injected CO_2 will diffuse into the periglandular spaces and the stroma will stand out in contrast as a dense homogeneous mass which is being distorted by an encapsulated tumor of the

areas on ordinary roentgenograms, in aeromammograms they project as dense, homogeneous, encapsulated masses from the matrix and have no connection with the skin or muscles (Fig. 16). The periphery of the tumor is rather dense and will frequently be separated from its

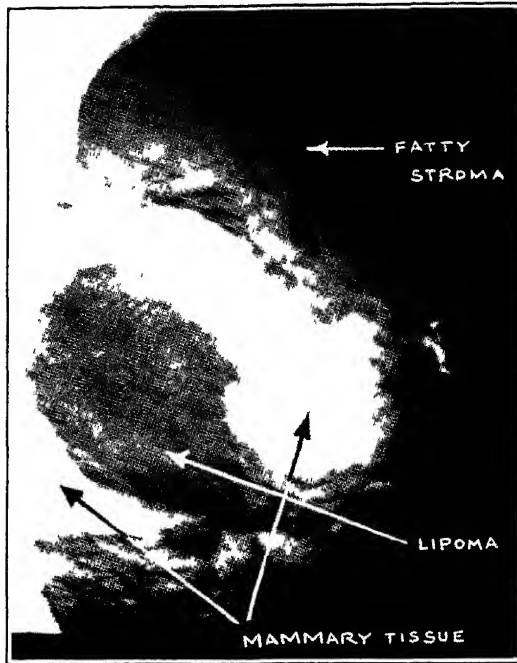


Fig 15—Lipoma The white homogenous matrix is being displaced by a large encapsulated tumor which has the same radiolucency as the fatty tissue stroma (Am J Roentgenol, March, 1938)

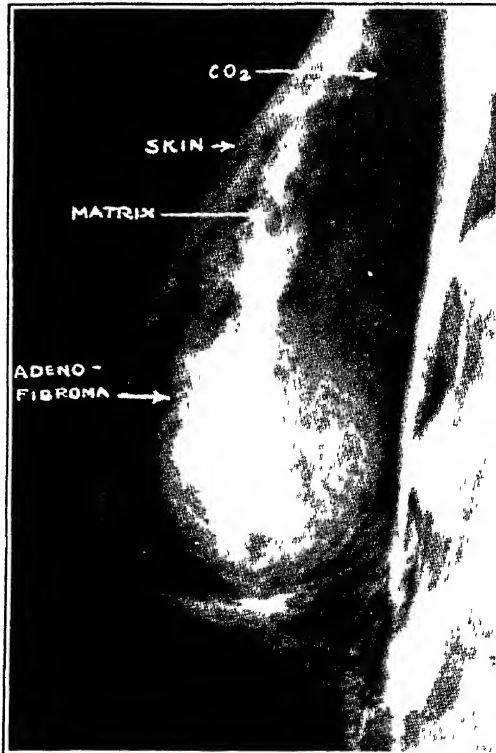


Fig 16—Fibroadenoma A firm, dense, encapsulated tumor can be seen arising from the matrix following CO₂ insufflations (Am J Roentgenol, March, 1938)

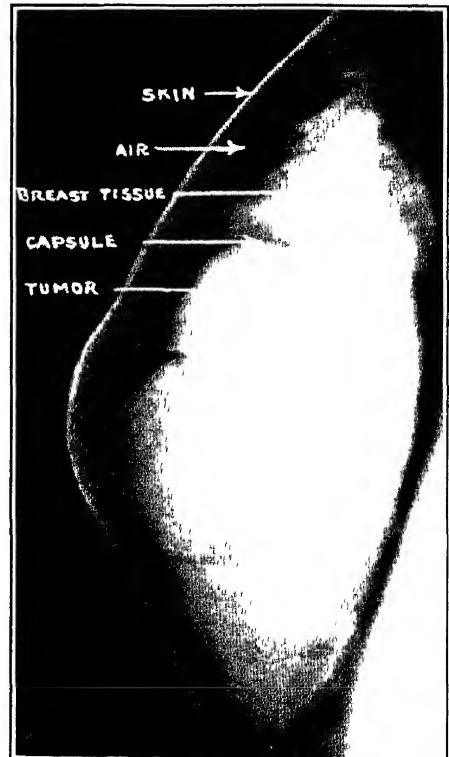


Fig 17—Shows how the air can outline the capsule of a fibroadenoma (Am J Roentgenol., March, 1938)

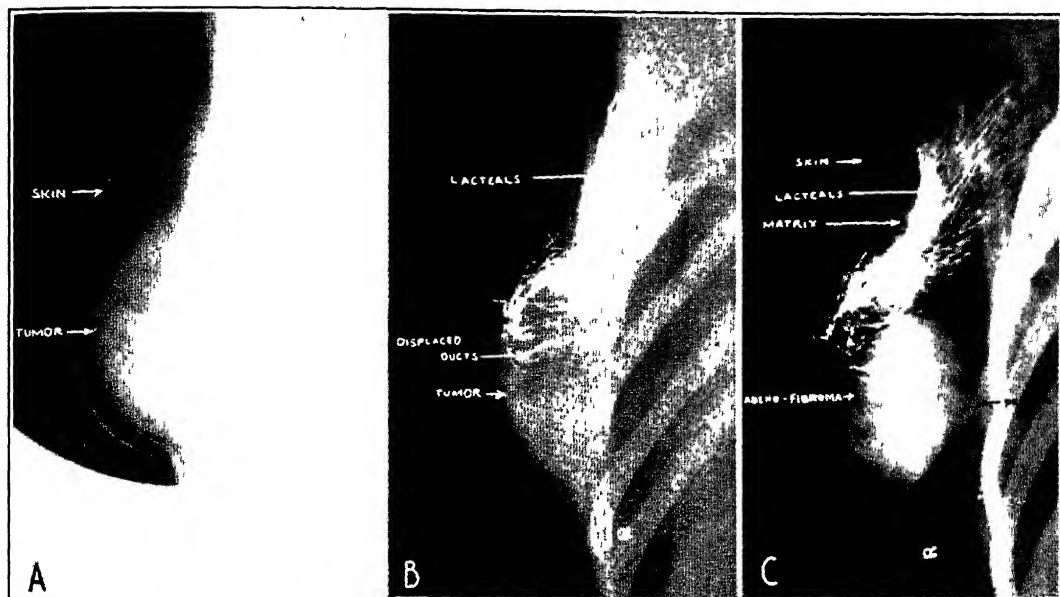


Fig 18 *A*, Roentgenogram shows a dense well-encapsulated tumor without denoting its origin *B*, The ducts do not communicate with the tumor but spread over its surface and then ascend into the axilla Displacement of the ducts indicates benignancy *C*, Combined thorotrast and CO₂ visualizations reveal the duct-bearing part of the gland to be normal, while a dense encapsulated tumor can be seen arising from the lower matrix Observe the accessory vascular pedicle attaching the neoplasm to the chest wall (Am J Roentgenol, March, 1938.)

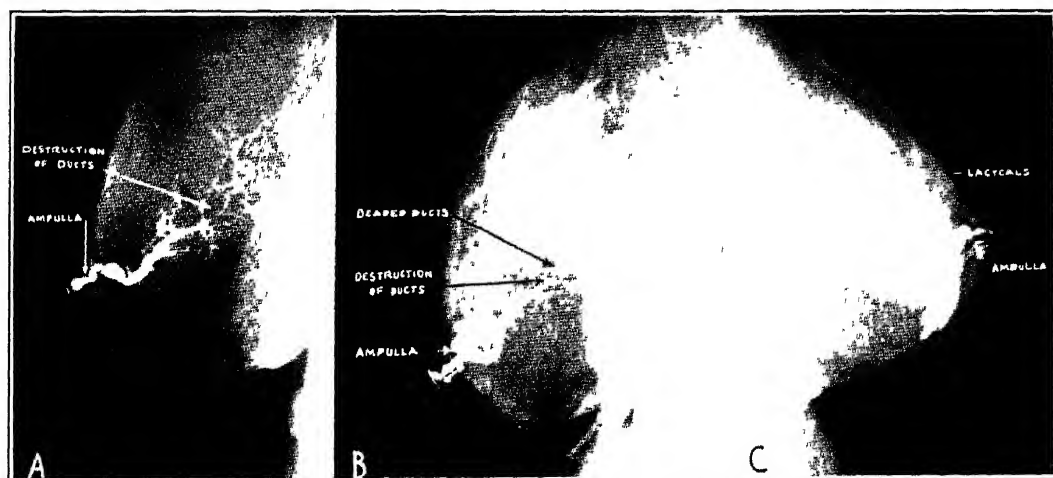


Fig 19 *A*, One duct injected with thorotrast Its outer segment is normal but the ramifying lacteals are displaced, invaded and destroyed Note the "beading effect" due to invasion *B*, Two ducts were injected with thorotrast and the same destructive invasive process is seen The ducts appear like a filamentous spiderweb *C*, Note the dense network of dilated, convoluted, branching ducts which the asymptomatic right breast has as compared with its malignant mate (Am J Roentgenol, March, 1938)

matrix bed by an encircling film of CO₂ (Fig. 17). Occasionally the fibrous tissue will be arranged in whorls. While the regional ducts are usually distorted or displaced by the expanding tumor, there is no interruption in the continuity of the striations and none of them traverse the mass. There is no evidence of invasion of contiguous structures or extension into the axillary space (Fig. 18).

Malignant Lesions—Malignant lesions produce characteristic deformities of the mammary gland which are recognizable by roentgenographic studies. Because of their destructive nature, these tumors produce definite alterations in the normal architectural configurations of the breast. Unfortunately, however, they possess the same radiodensity as the parent tissue and hence cannot be sharply differentiated from neighboring structures unless contrast mammograms are employed.

If the milk ducts of the tumor-bearing lobule are injected with thorotrast, the true nature of the invading neoplasm can be determined. Benign lesions distort the regional ducts by mechanically displacing or compressing them but malignant lesions invade, obstruct and destroy these ducts. The neoplastic cells displace the contrast medium and produce a characteristic "beading effect." If the carcinoma has obstructed or destroyed the ducts, the terminal radicals will not be visible and there will be a break in the ductal continuity. Rather than forming a dense mosaic of smooth walled, regularly branching ducts as in the normal breast, which is used as a control, these malignant processes cause the ducts to appear as a beaded, filamentous cobweb (Fig. 19).

The authors discuss malignant breast lesions in detail and illustrate various forms of carcinoma with well-chosen mammograms and aeromammograms.

Mammographic studies have forcibly emphasized several important points which should be considered in the surgical treatment of mammary carcinoma. In the first place, the visualized milk ducts very closely approximate the skin, sometimes being contiguous with it. It is essential, therefore, that reflected skin flaps should be thin and not contain much adipose tissue so that no glandular substance will be adherent. Second, the lactiferous tabules occasionally descend into the epigastric notch, pass across the midsternal line, and invariably ascend into the axilla. Hence the entire glandular and muscular tissue of this area should be removed and no remnant of mammary tissue should be overlooked. Third, the milk ducts may penetrate the pectoral muscles and their fascia and extend into the retropectoral space, making it essential to remove these muscles. Haphazard and incomplete surgery is of no value and, unless all breast tissue is removed, no operation should be attempted.

SIALOGRAPHY

Its Technic and Application in the Roentgen Study of Neoplasms of the Parotid Gland²

In a series of 125 cases studied at the Memorial Hospital in New York the authors have injected Steno's duct with radiopaque oil. Their roentgen findings in normal parotid glands and in those with various neoplasms are described in detail.

1—The technic, indications, and contraindications are discussed. The technic is a comparatively simple procedure for which no special paraphernalia are required.

2—Experimental studies on the normal gland have demonstrated the fact that lipiodol injections of not less than

1 cc. and not more than 1.75 cc. render the most satisfactory roentgen visualization of the parotid gland. Because of variability in the size and capacity of the duct system, an arbitrary rule has been formulated which permits variation in the amount of lipiodol used and requires that 3 to 5 times as much lipiodol be injected as the amount producing discomfort or pain.

3—In the normal, the lipiodol empties from the gland in 1 to 3 days. In abnormal conditions it may remain in the gland for periods longer than 2 weeks.

4—This roentgen study is based on an analysis of various neoplastic conditions in 76 cases, in all of which the clinical, the operative, the histological and the roentgenographic findings have been correlated.

5—The use of this procedure in mixed tumors of the parotid is discussed. The roentgen findings, depending on the various locations of the tumor, are presented. Sialography has made it possible to determine the operative plan before operation more accurately than has been heretofore possible.

6—The roentgenographic changes caused by infiltration, as observed in 62 per cent of the cases in this series, are described. We believe that when this picture of infiltration is observed it is diagnostic of carcinoma.

7—Illustrations of the various points discussed are presented.

INJECTION OF THORIUM DIOXIDE SOLUTION

Study of Its Effect When Injected into Rabbits³

The authors investigated thorium dioxide solution for the purpose of determining: (1) the site of storage; (2) the delayed effect on body tissue; (3) the

degree of radioactivity; (4) the rate of elimination; (5) the route of elimination. Three groups of rabbits were used in the experimental work. The findings are summarized by the authors, as follows:

1. Injected thorium is engulfed by the reticuloendothelial system, *i. e.*, the reticulum cells of the splenic pulp, lymphatic tissue, and bone marrow, the endothelial cells of the liver capillaries (Kupffer cells), lymph sinuses, splenic sinuses, bone marrow, and suprarenal capillaries, and the phagocytic cells in connective tissue.

2 There has been no evidence of elimination of this substance from the body during a 4-year period of observation. This apparently results in a permanent blockage of the reticuloendothelial system, and may thus impair its immunologic properties.

3 Thorium dioxide solution has been demonstrated by means of shadowgrams, to be definitely radioactive in both prepared ampules and when engulfed in body tissues. Even minute amounts of injected tissue have been shown to be radioactive by means of histoskiagrams and by the spinthariscopes. The use of filters has shown both alpha and gamma radiation are present.

4 The following histologic changes have invariably been found:

(a) The reticuloendothelial system phagocytoses the thorium dioxide.

(b) The liver shows pathologic changes varying from simple cloudy swelling to profound necrosis, depending upon the dose. These changes are followed by fibrous tissue proliferation giving a picture similar to mild nodular hyperplastic cirrhosis.

(c) The spleen shows damage varying from degeneration of the lymph follicles to marked necrosis, even of the vessels and interstitium.

(d) The bone marrow contains large clusters of thorium and shows hematopoietic depression.

(e) The lung histocytes contain thorium with no definite tissue damage.

(f) The adrenals contain thorium in the reticuloendothelial cells. There is questionable degeneration of the cortical cells in the zona glomerulosa.

The authors conclude that thorium dioxide solution should not be injected into human beings because

1. It is not eliminated from the body.

2. It apparently blockades the reticuloendothelial system and may thus adversely affect some of the body's immunity mechanism.

3. It may, as in our experimental animals, profoundly damage the liver and spleen parenchyma, with early and late degenerative changes.

4. It is a radioactive substance, and undoubtedly has dangerous cumulative radioactive effects

Histopathologic Study of Tissues of 65 Patients Injected with Thorium Dioxide Solution for Hepatosplenography⁴

Thorium dioxide solution has been used by the authors as a contrast medium in arteriography and hepatosplenography in several hundred cases over a period of 6 years. During this time no permanent harmful effects and extremely few immediate alarming reactions have been observed. The following objections to its use may be raised

1. It is retained for years in the reticuloendothelial cells of the body.

2. It possesses some radioactivity.

3. There is a possibility that it may be productive of malignant growth of cells when injected into the subcutaneous tissue

Because of the slowness with which the effects of radioactive substances de-

velop, the authors feel that 6 years of observation is not enough and several more years must elapse before it can be determined whether or not thorium dioxide solution in the amounts employed has any harmful effects. Until such time, caution should be observed in its use; small doses for arteriography, larger doses for hepatosplenography, and then only in those patients whose residual span of life is probably limited to a few years

The preparation used by the authors is a stabilized colloidal solution of thorium dioxide containing approximately 22 per cent of metal by volume. This substance when injected into the blood stream is rapidly removed and engulfed by the reticuloendothelial cells throughout the body. These cells, being most numerous in the liver and spleen, allow these organs to be demonstrated on x-ray films, since thorium is radiopaque due to its high atomic weight. The usual dose employed by the authors has been 75 cc. given in divided doses of 25 cc. each on 3 successive days. This amount of solution contains a quantity of thorium equivalent, in alpha ray activity to 1.5 to 3.0 micrograms of radium. The beta and gamma ray activity is probably insignificant.

Summary of Follow-Up Study of Patients—1

Ten patients have been reported from among a large number still alive years after the injection of thorotrast for the making of hepatosplenograms. These 10 patients have lived from nearly 4 to 6 years after the injection of the contrast medium. Some of the patients have very serious diseases such as leukemia and cirrhosis of the liver. In 2 patients subcutaneous nodules resulted from accidental injection of the thorium dioxide into the tissues of the arm, but there is no evi-

dence of neoplastic reaction adjacent to the nodules.

2 The liver and spleen still cast excellent shadows but there is evidence of mobilization of the thorium from these organs with its deposition in adjacent lymph nodes.

Histopathologic Study—When any foreign substance remains in the tissues for a long time, we must consider possible injury to the tissues. Certain inert substances, as carbon, have little or no injurious action on the tissues; others, as silicates, have a decidedly injurious action. Of outstanding interest at present is the action of certain specific carcinogenic substances obtained from coal tar, such as dibenzanthracene. The specificity of these various agents is of great importance.

It is well known that radioactive substances have an injurious action on the tissues. The radioactive ores of the Schneeberg and Joachimsthal mines are known to produce bronchogenic carcinoma. Necrosis and sarcoma of the bones in watch-dial painters are another familiar example.

Undoubtedly there is a potential danger in the injection of thorium dioxide into the tissues. Taft has been able to measure the gamma ray emission from thorium dioxide solution by means of a Geiger counter. His results show that 1 clinical dose of 75 cc. gives the gamma ray activity equivalent to 1.37 micrograms of radium.

A number of workers have considered the formation and retention of degradation products of thorium which emit alpha rays that are very toxic to tissues. There are numerous reports of animal experimental work in which damage was done by injected thorium dioxide.

With this evidence of the potential danger of the diagnostic injection of thorium dioxide before them, the authors

have studied the tissues of their patients who had received such injections. Two factors have been considered: (1) Length of time after injection; (2) diseased condition for diagnosis of which the injection was made. In 64 cases coming to necropsy and studied histologically the authors have selected 8 typical cases to report in detail with photomicrographs. In all cases, the picture is very much the same, with the granules of thorium dioxide scattered diffusely in the liver in the earlier months after injection, and some tendency to accumulate about the central veins and in the portal areas in the later months after injection. There is little indication of any shifting in the spleen from the early to the later months. In no case was there any evidence of cellular reaction or injury to the tissues that could be ascribed to the presence of the thorium dioxide.

In view of the reports by various workers of injurious effects following injection of thorium dioxide into the subcutaneous tissues of animals, the authors have examined a nodule removed from the arm of a young girl who had been injected 4 years and 5 months previously. Injection of 8 cc. thorium dioxide solution had been done for the purpose of ruling out rupture of the spleen following an automobile accident. At the time of injection some of the solution had accidentally leaked out of the vein into the subcutaneous tissues. Microscopically the nodule showed strands of dense hyaline connective tissues, separated by abundant masses of grayish brown granules of thorium dioxide. Nowhere was there any evidence of injury to the tissues nor cellular reaction other than the primary reaction resulting in the walling-off of the thorium dioxide.

Post-mortem Findings and Radioactivity Determinations 5 Years After Injection of Thorotrast⁵—

There has been considerable discussion as to whether or not thorotrast should be used for visualization in radiography of the liver and spleen. Thorotrast contains "25 per cent by volume of thorium dioxide (19 to 20 per cent by weight), about the same amount of protective colloid, said to be of a carbohydrate nature and further defined as a dextrin preparation. It contains as a preservative 0.15 per cent of methyl P-hydroxy benzoate "

A 73-year-old white woman was injected with 25 cc. of thorotrast on each of 3 successive days in June, 1932. X-ray examination at that time showed slight enlargement of the spleen but definite enlargement of the liver was not seen on the films. The patient died in June, 1937, 5 years after the thorotrast had been injected. On post-mortem examination collections of thorium dioxide particles were found in liver, spleen and perihepatic lymph nodes. There was also fibrosis in these structures and the authors believe it was due to the action of the thorotrast. Photomicrographs are shown by the authors to demonstrate these changes of fibrosis and deposition of thorium dioxide.

Later the liver was ashed and tested with a Geiger counter for radioactivity. This test showed that the liver retained 27 per cent of the gamma-ray activity of the 75 cc. of thorotrast or approximately equivalent to 0.3 microgram of radium.

SKIAGRAPHY OF THE CHEST⁶

The use of roentgenography as an aid to diagnosis may well be regarded as the greatest advance in medicine during the present century, worthy to rank with

the discovery of antiseptics and anesthetics. Roentgenography of the chest has become a most important and, indeed, an indispensable adjunct in diagnosis. Its routine application has often enabled a diagnosis of pulmonary disease to be made, even when the symptoms were referred to some other organ—for example, cases of so-called indigestion and gastritis or suspected appendicitis.

The importance has been emphasized of a careful examination of the patients, based upon history, symptoms, and the routine use of the standard methods of diagnosis. By such means, the careful and experienced practitioner can diagnose accurately a fair proportion of diseases of the chest from which his patients are suffering, while the consultant's wider experience of particular conditions will raise the standard of diagnosis still further. It is well known that more mistakes in diagnosis are due to failure to make a thorough examination of the patient than to lack of knowledge. The increasing popularity of roentgenography based on a growing appreciation of its value in the elucidation of difficult cases, ought not to permit any relaxation in the thoroughness with which the older methods of examination are employed.

It is well known, as Sampson and Lawrason Brown and others have shown, that radiographs frequently reveal the existence of pulmonary disease in the apparent absence of any physical signs, even when the patient is examined by an experienced physician. There are many cases, on the other hand, in which radiographic examination alone, in the absence of information derived from a careful history and physical examination, may provide information which is equivocal or misleading. Accurate diagnosis depends upon a careful appraisalment of all the available evidence including history and clinical, laboratory, and radio-

logical examinations. As Sir Arthur MacNalty has said, "pulmonary tuberculosis still reveals itself by physical signs and symptoms; in other words, inspection, palpation, percussion, and auscultation are not displaced, but reinforced, by a skiagram of the chest."

Pulmonary tuberculosis should be regarded as at least a possibility, and radiographic examination employed, in the following circumstances:

1. In cases provisionally diagnosed as bronchitis which do not clear up within 4 weeks.

2. Where patients complain of indigestion and dyspepsia. Many so-called gastric or duodenal ulcers are really manifestations of tuberculous toxemia.

3. In cases of alleged hemoptysis.

4. In young persons with symptoms of debility or anemia.

5. In cases of chronic hoarseness

6. In cases of ischio-rectal abscess

7. In all cases where there is a clear history of tuberculosis in some member of the family

8. Where there is a history of some close association with a case of pulmonary tuberculosis—for example, friend or workmate in office or factory.

9. Where a case of tuberculous meningitis or other form of nonpulmonary tuberculosis is found, attention should be directed to adult members of the household, even if stated to be in good health, in order to discover a possible source of infection.

When a diagnosis of *pulmonary tuberculosis* has been made, radiological examination is often of great value

1. To determine the extent and nature of the disease—for example, unilateral or bilateral, presence of cavities, fibrosis and calcification. The information thereby obtained is often of great assistance in deciding the nature of treatment.

2. During the course of treatment serial radiography is essential in artificial pneumothorax and whenever surgical measures are contemplated—for example, phrenic operations, division of adhesions and thoracoplasty.

3. Serial radiography also is of great service in enabling the progress of the disease to be readily ascertained, as well as providing opportunities for the study of "living pathology."

Apart from the question of tuberculosis, radiographic examination of the chest is important in the differential diagnosis of chronic bronchitis, bronchiectasis (especially when used in conjunction with injections of lipiodol), pleurisy, pneumonias, abscesses, malignant disease, and silicosis. Caution must be exercised in the interpretation of roentgenograms of the chest, as the appearances, for example, in cancer, tuberculosis and silicosis may at times be indistinguishable. An opacity may be due to fluid, thickened pleura, consolidation, atelectasis, abscess, or underlying new growth. Consistently accurate diagnosis is only possible when roentgenography is correlated with clinical evidence. It demands judgment and experience.

The author gives some interesting facts regarding the procedure used in the Lancashire area with which he is associated as radiologist. The population of the area is about 370,000 and is mainly urban. There are 5 tuberculosis dispensaries and 1 small hospital of 57 beds for adult male pulmonary cases. The medical staff consists of 3 tuberculosis officers working as a team. The x-ray equipment is located in the central dispensary. Roentgenograms are taken with a standardized technic in one-tenth second at a distance of 4 feet.

Two afternoon sessions are held each week. On the same afternoons a pneu-

mothorax clinic is arranged so as to have the patients checked up for the degree of collapse by fluoroscopic examination. During each x-ray session, 2 medical officers work together, 1 as clinical radiologist, the other giving useful help in chest, throat and other examination. On the morning following each x-ray session the 3 tuberculosis officers meet as a board to examine the films. It is obviously advantageous to bring the clinicians and radiologist so closely together to discuss cases of special difficulty or interest. After the diagnosis is made a report is sent to the patient's doctor, and in many cases reduced prints of the roentgenograms are sent along with the report. The author feels that these prints are greatly appreciated and help to encourage the physicians to send their patients to the clinic for diagnosis and follow-up.

Serial Roentgen Examinations of the Chest in University Students⁷

The authors have made roentgenograms of the chests of 2719 students in the University of Wisconsin in an attempt to discover early cases of pulmonary tuberculosis. Previous investigations by other authorities, in which groups of school children, students, state police, soldiers and sailors have been examined systematically by roentgenograms, have demonstrated the fact that a small percentage of active tuberculous lesions were found which could not be detected by physical examination.

With the facilities at hand it was deemed impossible to take x-ray films of all the 2000 to 2500 new students enrolled each year in the University of Wisconsin. The Student Health Service consequently did Mantoux tests first. All of the positive reactors were then referred for the roentgen examination.

The results of examinations conducted in the years 1934, 1935 and 1936 are reported in tabular form.

Of the students who had previously shown positive Mantoux reactions, there were 76 per cent in whom the roentgenograms failed to show any evidence of pulmonary tuberculosis.

There were 21 per cent showing calcifications in the lung parenchyma (Ghon tubercle), in the hilum lymph nodes, or in both. Such calcifications were considered to be evidence of a previous first infection or childhood type. Nearly 3 per cent of the students examined by x-ray showed adult type of lesions in the lung parenchyma and thickening of the apical pleura. The authors consider apical pleuritis in this age group to have more significance than in patients of more advanced age. In order to be classed as tuberculous apical pleuritis, a band of increased density over the summit of one or both apices had to show a rough and irregular lower margin.

In some roentgenograms, fine trunk markings could be traced up to, and merging with, the band of increased density. Progress films at suitable intervals are indicated in some of these cases as it was found to be difficult to determine whether the lesion was confined to the pleura or whether there was involvement of the subjacent lung parenchyma. Progress films helped in deciding whether the thickening was of recent inflammatory nature or was older and consisted of fibrotic scar tissue.

Nearly all types of tuberculosis were discovered. Some were unquestionably active, as evidenced by the softness of the shadows, and some were so far advanced as to show cavitation.

In regard to the extensiveness of the involvement, it was found that some lesions were evidenced by small round

or wedge-shaped opacities, while in other cases half of both lungs was diseased.

In 1 student, multiple calcified hemogenous foci were found.

The authors have listed some of the abnormalities discovered which were not related to tuberculosis. Among these of definite clinical importance is bronchiectasis; while abnormalities of the heart, thickened pleura, and resected ribs might in some cases have significance.

THE VALUE OF RADIOLOGY IN THE ELUCIDATION OF HEMOPTYSIS⁸

Hemoptysis formerly was considered to be a certain indication of pulmonary tuberculosis unless the contrary could be proved. We know now that it may be a sign of any chronic or acute disease from simple bronchitis to lobar pneumonia.

Hemoptysis in Pulmonary Tuberculosis

When pulmonary tuberculosis has been responsible for a hemorrhage from the lungs, a chest roentgenogram will nearly always supply evidence of this disease. In some cases the lesions of pulmonary tuberculosis may not be demonstrated in the usual P A position and lateral and oblique positions may be necessary to reveal small foci located behind the heart, lung roots, or diaphragm.

Tomography may reveal small foci or cavities which cannot be demonstrated by any special position of the patient.

There are many other conditions besides pulmonary tuberculosis which may cause hemoptysis, the most important being bronchiectasis, heart disease, new growth, aneurism, and trauma. A frank hemoptysis may also occur in early pneumonia. Vinson, of the Mayo Clinic, reported on the relative frequency of hemoptysis in tuberculosis, bronchiectasis

and mitral stenosis. In 3 groups of 100 patients with each of these diseases it was found that there were 49 cases of hemoptysis in 100 patients with bronchiectasis, 29 cases of hemoptysis in 100 patients with tuberculosis, and 18 cases of hemoptysis in 100 patients with mitral stenosis.

Dry Hemorrhagic Bronchiectasis

The occurrence of hemoptysis in bronchiectasis has been known for a long time, but it is only since the introduction of lipiodol as a method of outlining the bronchi that the presence of what is termed "dry hemorrhagic bronchiectasis" has been successfully demonstrated. In this condition there are no obvious physical signs such as clubbing of the fingers or purulent sputum. The preliminary radiographs may show evidence of fibrosis, or the dilated bronchi may be demonstrated as a series of spherical or cylindrical clear spaces.

Injection of lipiodol will be necessary in order to determine the extent of the bronchiectasis. The lesion may be found either in the upper part of the lung, where it closely simulates pulmonary tuberculosis in appearance, or, more commonly, in the lower lobes, where it is less likely to be confused with other lesions. When the condition is developmental in origin and probably due to failure in budding, the dilatations are spherical in appearance, while in the acquired disease the dilatations are usually cylindrical.

Hemoptysis in Heart Disease

When examining any patients with hemoptysis, it is essential to consider cardiac disease as one of the possibilities. As previously mentioned, mitral stenosis is the next most frequent cause of hemoptysis besides tuberculosis and bronchiectasis. Paroxysmal attacks of hemorrhage may occur in mitral stenosis due to con-

gestion in the lungs or to infarction. In an early case of mitral stenosis, the first evidence to be recognized in an anterior roentgenogram is a prominence of the pulmonary artery and pulmonary conus. Some enlargement of the left auricle may be detected at this stage in an oblique film. As the degree of stenosis increases there is a progressive enlargement of the left auricle, which can be seen bulging into the retrocardiac space in radiographs taken in oblique and lateral positions. The accompanying congestion in the lung fields is a characteristic feature.

Pulmonary Infarction

When hemoptysis occurs with vascular engorgement of the lungs, the conditions to be considered in a differential diagnosis are mitral stenosis, left ventricular failure, postoperative congestion, and infarction. The evidences of pulmonary infarction to be recognized in a roentgenogram were not well known before the advent of portable x-ray apparatus. As the patients are usually very ill, the condition is rarely seen in the routine radiographs taken in the x-ray department. The changes are usually seen at the base of the right lung. The appearances are variable, and may consist of an area of clouding, rather like the appearances seen in pneumonitis; or an irregular shadow may be present resembling that seen in lung abscess. An accompanying pleural effusion may mask the area of consolidation in the lung. In the absence of pleural effusion the heart is usually drawn slightly toward the side of the lesion.

Bronchial Carcinoma

Frank hemoptysis is uncommon in bronchial carcinoma because the lumen of the bronchus is filled with necrotic material, and not sufficient blood is present to be obvious in the sputum.

In malignant papilloma, benign papilloma and endotheliomas, hemorrhage is rather common and may be profuse. A bronchial carcinoma usually produces changes in the lungs that are easily demonstrated in a roentgenogram. Benign growths, on the other hand, will not be detected unless large enough to block the lumen and cause atelectasis.

Tracheal varix and nonspecific granuloma have been mentioned in the literature as a cause of hemoptysis. Tracheal carcinoma, although rare, has also been mentioned. If roentgenological examination is negative and the attacks of hemoptysis continue, a bronchoscopic examination should be made.

Aneurism of the Aorta

In aneurism of the aorta, hemoptysis occurs as a terminal event, staining of the sputum being a warning sign of the imminence of a rupture. The diagnosis of aneurism is not always easy for the clinician, especially if the posterior part of the arch or the descending thoracic aorta is involved. Unfortunately, it is not always easy for the radiologist either, for any growth or tumor in the neighborhood of the aorta may simulate an aneurism. Kymography is of great assistance in such cases in separating the outline of the aorta from that of the tumor.

Hemoptysis Following Injury to the Chest

Hemoptysis may follow injuries to the chest with or without fracture of ribs. In severe injuries fractures of ribs are easily demonstrated in roentgenograms. In less severe injuries the rib fractures may not be demonstrated on films taken in the usual manner. In such cases oblique films taken for the particular area where pain is the greatest may serve the purpose better.

HYSTEROSALPINGOGRAPHY IN GYNECOLOGIC DIAG- NOSIS⁹

Many of the pathologic conditions with which the gynecologist must contend involve the cavities and linings of the uterus and tubes, and hysterosalpingography offers the best and simplest means of locating and estimating the extent and severity of these conditions. The author has gained experience from more than 1200 injections of iodized oil and is convinced that hysterosalpingography, when properly carried out, is safe and is only a minor procedure from the patient's standpoint. In all these examinations, there have been no catastrophies.

The contraindications are active, serious infection of the genital tract and normal pregnancy.

In making the injection of iodized oil strict aseptic and antiseptic precautions should be observed. The technic is simple and is given in detail by the author as follows:

"The patient is placed in lithotomy position over a Bucky diaphragm at the end of a table which has stirrups. A good light reflected into the vagina is necessary. A vaginal speculum is inserted, and the vagina and cervix are cleaned of discharge. Tincture of iodine is applied to the cervix and to the external os. The anterior lip of the cervix is then grasped with a single tooth volsellum to hold it in a fixed position. The oil-filled, short-tipped cannula, attached to the syringe, is inserted into the external os, pressing the acorn of the cannula gently against its opening, and the oil is injected slowly into the uterine cavity. When the cavity is filled, the oil will proceed into the tubes if they are patent. At this time the patient will experience painful uterine contractions, and the oil will leak backward between the acorn of the cannula

and the cervical opening. The amount of oil required for the injection is usually from 5 to 8 cc. (more, however, if the uterine cavity is large, and less if it is small). The amount of pressure used in the injection should be scarcely more than that used in giving any injection through a syringe. By observing this precaution there can be no danger of excessive pressure. Once the cavity is filled, the roentgenogram is made with the cannula still in position; then the cannula is removed and the oil is allowed to run from the cervix. This completes the injection which, with exposure of the film, usually takes 2 minutes after the vaginal speculum has been inserted. By using the short-tipped cannula, the position of the uterus or the direction of the canal need not be known, and sounding of the uterus is unnecessary since the short-tipped cannula does not extend to the internal os.

It always is well to describe the technic to the patient, and to advise her that she will be told in advance of each pain—that associated with the grasping of the anterior lip with the volsellum, and that associated with the insertion of the cannula, and that associated with the filling of the uterine cavity. When she is so advised, and is told further that the entire procedure will be over in 2 minutes, her discomfort is lessened, expectation of severe pain is prevented, and co-operation is assured.

Another roentgenogram should be taken from 8 to 24 hours later if one wants to know about the patency of the tubes. By this time the tubes and uterus will be empty of the oil, and if the tubes are patent there will be some filmy traces of oil in the pelvic cavity. In the cases in which the tubes are closed, the actual site of the closure will be seen in the cornu, in the tube proper, or at the distal extremity. All the cavities of the uterus

and tubes reached by the oil will be visualized with the roentgen ray. The author shows a hysterosalpingogram of a normal uterus and tubes. The uterine cavity is smoothly outlined and approximately triangular in shape. The cervical canal is open and free from filling defects. The fine, hazy, tortuous shadow of a fallopian tube extends from each upper horn of the uterine cavity. The author shows hysterosalpingograms which illustrate deformities of the cervical canal and defects of the body of the uterus. Other hysterosalpingograms illustrate congenital defects. In ectopic pregnancy, the iodized oil shows a small uterine cavity, thus proving definitely that the pregnancy must be outside the uterus.

The patency or nonpatency of the tubes is one of the most helpful aids to diagnosis which can be derived from hysterosalpingography. The lumen of a normal tube has a characteristically fuzzy appearance, while the lumen of a chronically diseased tube will have a sharply outlined, wiry appearance. In differentiating between a tubal mass and an ovarian mass, if the tube fills normally to its distal extremity it can be excluded as the site of the mass. Small hydrosalpinges which cannot be detected with bimanual examination are often revealed by hysterosalpingography.

CANCER

Surgery and Radiotherapy in Treatment¹⁰—Although the surgeon is probably more tolerant of change today, he still tends to eye with suspicion anything that represents very much of a departure from the established habit. This is especially true when changing trends seem to threaten the removal of certain diseases in part or in whole from the previously accepted fields of operative surgery.

Probably in no field of surgery is this so well illustrated as in the treatment of malignancy. In 1913, articles in *Surgery, Gynecology and Obstetrics* from the clinics of distinguished surgeons voiced the general feeling of the time when they stated that the greatest hope in treating carcinoma of the cervix uteri lay in wide excision of the primary growth. In 1938, just 25 years later, the bulk of evidence indicates without doubt that radiotherapy, with radium and the roentgen ray in combination, gives far better results than radical surgery, now, or at any time in the past. Some surgeons, however, still persistently adhere to the use of radical operations of the Wertheim type in at least a part of the patients whom they are treating who are suffering with carcinoma of the cervix. They give ground grudgingly.

Twenty-five years ago carcinoma of the breast was treated almost exclusively by surgery. Today radical surgery is still the method of general choice but evidence indicating the value of radiotherapy is accumulating so rapidly and surely that in some form it is commonly employed as a supplementary procedure. Some surgeons are so dissatisfied with the effectiveness of radical mastectomy and so impressed by the evidence indicating the benefits of radiation therapy that they are treating certain groups of patients with locally administered radiotherapy alone. Others, in search of still more effective therapy, are investigating the supplementary treatment of mammary cancer, especially in younger women, through sterilization by x-radiation of the ovaries. This form of therapy may foreshadow the accumulation of more evidence that carcinoma is a local manifestation of a systemic abnormality and, hence, may be solved by some type of systemic therapy rather than by local therapy.

Carcinoma in many parts of the body might be mentioned to illustrate still further the changing trends in surgical and radiation therapy. The common factor in each instance, however, is the improvement in the character of available radiant energy and the betterment in the methods of its application. Higher voltage x-ray machines, better methods of filtration, more general availability of radium element and emanation and many other technical advances, as well as the training of more experienced radiotherapists, will give a real impetus to radiotherapy as a therapeutic agent in the next few years. The recently developed cyclotron, which makes it possible to imbue almost any substance with radiant energy, opens a field of unlimited possibilities. A great number of animal experimentations and clinical investigations, of course, must be carried out before its usefulness can be definitely determined, but if it is established it may well revolutionize the treatment of malignant tumors.

The fundamental evaluation of, and comparison between, surgery and radiotherapy can be carried out most successfully only through close association between the surgeon, the x-ray therapist, the radium therapist, the surgical pathologist, the post-mortem pathologist, and the experimental physiologist. This association perhaps reaches its ideal in the "tumor clinic" type of organization. In such a group, the patient with a tumor and the patient that has been treated for a tumor are observed and data recorded so that the results in the individual and in series of individuals may be studied and compared. Each physician contributes of his own specialized knowledge of the disease and benefits through the correlation of various viewpoints. Through this kind of concerted effort will come the basis for the establishment of im-

proved methods that will be a credit to both the surgeon and the radiotherapist in the safest and best management of the patient with cancer.

Principles Governing Radiation Therapy of Cancer

In a discussion of treatment of cancer by irradiation, G. T. Pack¹¹ states that surgery, the actual cautery, and chemical cauterizing agents all have their place in removing or destroying cancerous tissues. Radiation therapy, by x-rays and gamma rays from radium, has definite advantages over these other methods in cases of cancer in which the cancer cells are more easily killed than are the cells of the normal surrounding tissues. Radiosensitivity seems to have some relationship to the origin of the cells making up the cancer. Tumors developing from primitive blood-forming tissues are likely to be radiosensitive, as, for example, lymphosarcoma, myeloma, endothelioma and angioma. Tumors developing from neural crest cells are likely to be radioresistant, as, for example, glioma, neurosarcoma, melanoma and mixed tumor of the parotid.

Methods of Radiation Therapy—Irradiation therapy may be applied by 2 methods:

- 1 From an external source.
- 2 From a source applied directly into the tumor or surrounding it.

External radiation may be given by x-rays with low voltage for superficial lesions and with high voltage or super-voltage for deeply seated lesions. Radium may be used instead of x-rays for the treatment of superficial lesions by means of small plaques, trays or moulages. Radium may be used for deeply seated lesions (telerradium therapy) by means of large quantities of radium in bombs or packs several centimeters away from the lesions under treatment.

Intracavitary Irradiation—Radium element in tubes, covered with sufficient platinum, gold, brass or aluminum for filtration, may be placed within body cavities for contact treatment of cancers of nares, orbits, antra, larynx, esophagus, uterus or vagina

Interstitial Irradiation—Radium needles and radon seeds may be driven directly into, or placed in groups surrounding, cancers in soft tissues. This method of treating accessible tumors is usually supplementary to external irradiation.

Units of Dosage—Pack has summed up the subject of dosage used in irradiation therapy concisely in the following words. "It is best to administer to all the neoplastic territory the maximal quantity of radiant energy compatible with the maintenance of tissue integrity. To speak intelligently of these quantities it is best to have some common physical and biological measures of the dosage. Thus in the case of radium the quantity of gamma rays at the source is known as the "dose of emission." One knows with precision the dose of emission because this is invariable. The dose emitted is expressed by 2 different notations. The one has for its basis the intensity of the gamma rays and the duration of their application, the intensity is proportional to the quantity of radium present; the dose is obtained by the product of the quantity and the time, which is expressed as milligram-hours of radium or as millicurie-hours of radon (gram-hours or curie-hours in the case of large bombs or packs). The other notation, which is utilized throughout France, makes the dose proportional to the quantity of radium emanation destroyed (disintegrated) during the course of its application. This is expressed in terms of "millicuries destroyed," or of "microcuries destroyed," the latter term con-

noting only one-thousandth of the former. The physical efficiency of 1 mc of radon throughout its life is equivalent to 133 mc.-hr. Therefore 1 mc. destroyed is equivalent to 133 mc.-hr. or 133 mg.-hr.

The dose of gamma or roentgen rays at the surface or the point of entrance into the body is the *superficial dose*, while the dose to the tumor by unit volume of the tissues treated is the "tissue or tumor dose."

The unit of x-ray dosage called the "roentgen" or r (designated always by small r) has been standardized and internationally accepted. The roentgen has been defined "*as that quantity of roentgen radiation which, when the wall effect of the ionization chamber is avoided and the secondary electrons are fully utilized, produces in 1 cc. of atmospheric air at 0° C and 76 cm. mercury pressure such a degree of conductivity by ionization that 1 electrostatic unit of charge is measured at saturation current*"

In the measurement of roentgen rays and gamma rays by biological means, the most common unit is the establishment of an erythema dose under certain conditions. Quimby, of the Physics Department of the Memorial Hospital, has defined and employed the term "threshold erythema," which is that dose of radiation that will cause a perceptible change in the skin of 80 per cent of the subjects and no discernible discoloration in 20 per cent in 2 to 4 weeks after the exposure to the rays. Quimby has found that the threshold erythema with 200 kv 100 sq cm field, 50 cm. target-skin distance, and filter of 0.5 mm copper and 2.5 mm aluminum is 500 to 525 r. The therapeutic erythema, on the other hand, varies with different radiologists from 600 to 1000 r."

The Tissue Dose—Cancericidal Dose—At the Memorial Hospital, the "threshold erythema" is used as the unit of tissue dosage. As mentioned above, this can be

determined for each x-ray tube and each radium applicator by direct experiment

At various depths below the surface of the tissue being irradiated the depth doses can be calculated as being various percentages of the dosage of the radiation falling on the surface. The method of determining these percentages is by making measurements with a small ionization chamber placed first on the surface of a vessel of water and then placed successively at various depths below the surface of the water. Such water phantom measurements agree fairly well with measurements obtained by placing the ionization chamber similar distances beneath the surface in various cavities in the human body. The data obtained by these water phantom measurements are plotted as "isodose curves" These isodose curves are used for rapid calculation of the depth dosage given to a tumor when irradiated by cross firing through several portals

In the case of interstitial irradiation the measurement by direct experiment is more complicated, especially as the irradiation is applied from numerous sources simultaneously At Memorial Hospital this has been worked out in a practical manner by Martin and Qumby They have demonstrated that in any sphere it makes little difference in the dosage at the periphery whether the source of radiation be concentrated at the center or be distributed uniformly within the inner half of the sphere. They have prepared tables for spheres of various sizes giving threshold erythema dosages at the periphery when various quantities of radon are placed near the center or at least within the inner half of the spheres.

The cancericidal doses for many different kinds of tumors have been determined by actual clinical observation and can be stated in terms of threshold

erythema dose (T. E. D.). For example, intraoral squamous cell carcinoma requires 6 to 8 T. E. D., while transitional cell carcinoma requires 2 to 4 T. E. D. for sterilization. By calculating external irradiation and interstitial irradiation in terms of the same unit it is convenient then to determine combined external and interstitial irradiation by adding the number of units applied in the 2 methods.

Prescription for Roentgen Therapy

For the safety of the patient roentgen-ray dosage must be prescribed in an accurate way and a detailed record should be kept of the treatment given. The quantitative factor should be expressed in r units and the qualitative factor in Angstrom units or by stating the half-value layer in millimeters of copper, aluminum or other metallic filters. In addition to these 2 factors should be specified the kilovoltage, filtration, target-skin distance, and time of application in minutes. The tumor depth below the surface should usually be indicated. The size and number of the portals through which treatments are given is also important as is also the factor of number of treatments and the intervals between treatments, for a single massive dose has an effect quite different from that of the same total dosage fractionated over several weeks or months

Kilovoltage (Potential) — As the voltage or potential applied to the x-ray tube is increased, the average wave length of the rays emitted becomes shorter and shorter Short waves penetrate tissues more readily than longer waves. This important factor is utilized in therapy of tumors deep below the surface by applying high voltages of 200 kv. to 1000 kv. For therapy of superficial skin diseases lower voltages are used All x-ray tubes give off rays

varying considerably in wave length. When the effect of short waves on deep tumors is desired, filters of copper, aluminum or other metals are employed to absorb the long waves, which would have an undesirable effect on the skin and superficial tissues.

Comparison of Teleradium Therapy with Supervoltage Roentgen Therapy—It has been estimated that supervoltages of over 1500 kv. would produce x-rays having wave lengths comparable to the gamma rays of radium. Already there are several 1000 kv. or million volt machines in use in the United States.

The roentgen rays produced by these machines have biological effects differing little, if any, from the effects which follow teleradium therapy with packs containing 4 Gm. of radium. The roentgen rays have far greater intensity and so can be used to treat more patients in a given time. This greater intensity may not be desirable, however, for therapy spread out over a longer period seems to have advantages.

The Effective Wave Length of Radiation—The wave length of roentgen rays depends upon 2 factors: the energy with which the electrons fly across the x-ray tube and bombard the target, and the atomic weight of the material of which the target is composed. The energy with which the electrons fly across the tube increases with the voltage applied to the terminals of the tube. The wave length of the roentgen rays becomes shorter as the voltage is increased. The higher the atomic weight of the target material the shorter the wave length of the roentgen rays emitted. Tungsten, of which most targets are made, has a very high atomic weight and emits characteristic rays of very short wave length. When roentgen rays emitted by the tungsten target enter the human body

they encounter secondary targets of much lower atomic weight, such as sodium, potassium and calcium. The secondary rays given off from these targets have much longer wave lengths and feebler penetration than the original rays. It is apparent that the way to get deep penetration, to deliver greater depth doses, is to raise the voltage applied to the x-ray tube. To put this into figures, Pack gives the following:

"Failla has found that the relative depth doses at 10 cm depth obtained under comparable conditions with 200 kv roentgen rays, 700 kv. roentgen rays, and gamma rays, are respectively 29.0, 41.2 and 56.7 per cent. Accordingly, from this point of view, 700 kv. roentgen rays are considerably better than 200 kv. roentgen rays, but not as good as gamma rays. This advantage is not realized in clinical practice because it is not practical to apply radium at the focal distances used in roentgen therapy."

Ionization in Tissues—The destruction of living cells by radiation is due to the release of electrons from the atoms, of which the cells are composed, when these atoms are bombarded by gamma rays or roentgen rays. Finally, the atoms, minus 1 or more electrons, combine with other electrons. In some cases the recombination is harmless to the cell but in other cases the recombination is a form of chemical change which brings about the death of the cell.

Current (Milliamperage)—The kilovoltage applied to the terminals of the x-ray tube determines the speed with which the electrons fly across the tube and strike the anode and determines the wave length of the x-rays emitted. In a similar manner the milliamperage is an indicator of the number of electrons flying across the tube. The more electrons flying across the tube the more x-rays are emitted from the anode in a

given length of time. Pack states this concisely in the following words:

"The usual roentgen tubes carry from 4 to 30 ma. Thus a tube running at 4 ma. for 25 minutes would deliver 100 ma.-minutes and a tube running at 25 ma for 4 minutes would also deliver 100 ma.-minutes or its equivalent in roentgens, other conditions remaining the same."

The Biological Action of Neutron Rays¹²—Lawrence describes the cyclotron by means of which he produces neutron rays by bombarding a beryllium target with high-speed deuterons. Neutron rays are really streams of tiny particles knocked out of the nuclei of the beryllium atoms. Each neutron consists of a proton and an electron in intimate association so that the positive electric charge of the one exactly neutralizes the negative charge of the other. Such neutral particles can pass between the orbital electrons of atoms more readily than can charged particles such as alpha particles, beta particles, or the secondary electrons dislodged by x-rays or gamma rays. The neutrons thus have fundamentally a different effect upon matter than have x-rays or gamma rays. Lawrence was interested in comparing the lethal effect of neutron rays upon living cells with the effect of x-rays upon similar cells. Further he was interested in finding out if there might be a different effect upon cancer cells than upon normal tissue cells.

Lawrence and his collaborators found that neutrons were 5 times as effective as x-rays in killing the cancer cells of mammary carcinoma of mice. In normal tissue cells of mice the lethal power of neutrons was only 3.8 times as great as that of x-rays. This difference between the effectiveness on cancer cells and upon normal tissue cells has en-

couraged Lawrence to continue experiments along this line.

Conservative Treatment of Cancer of the Breast¹³

In an address delivered to the American Surgical Association the well-known British surgeon Geoffrey Keynes discussed the reasons for some of the poor results obtained in treating cancer of the breast. He concluded as follows:

"The foregoing account of a clinical investigation, which has now extended over 14 years, seems to me to show that the treatment of carcinoma of the breast may justifiably be made much more conservative than it usually is, provided that the necessary facilities for irradiation are available. Statistics appear to demonstrate that a definite improvement can be obtained in the most favorable group of patients by judicious use of interstitial radium alone, or of radium combined with very conservative surgery. The rapid improvement in x-ray technic now taking place suggests that x-rays may perhaps be used as an alternative to radium according to circumstances. The treatment here advocated is, however, conservative rather than purely radiological and details of the technic will no doubt undergo further modification. The general trend of surgery in the treatment of cancer is away from the very extensive operations formerly in vogue, and I believe that this may be found to be true of the future treatment of cancer of the breast. My own results with conservative methods encourage me to proceed in that belief."

Combined operation and irradiation is the method of treatment advocated by the majority of radiologists and postulates thorough radical mastectomy followed by irradiation adequate to destroy all cancer cells in the bed of the tumor and surrounding tissues. Many radiolo-

TABLE I
RECENT COMPARATIVE STATISTICS FROM THE SAME CLINICS

Author	Operation Alone, Percentage Living 5 Years			Operation and Irradiation, Percentage Living 5 Years		
	No of Patients	Stage 2	All Patients Operated On	No of Patients	Stage 2	All Patients Operated On
Siemens, W.: Strahlentherapie 47 627 (Aug. 9) 1933	104	33.6		188	53.2	
Harrington*	604	24.3		1447	28.8	..
Gentil, Francisco, and Guedes, Bernard: Arq d pat. 2 122, 1928	42	20.6		83	42.5	
Adair		20.6	35.0		23.0	40.6
Hintze	656		30.5	183		53.0
Portmann	85		35.6	99		46.0
Ganz, Ernst: Strahlentherapie 57:413-414, 1936	3599		31.2	118		40.0

It can be seen that the end results were improved by postoperative irradiation, as compared with operation alone, from 11.4 to 73.7 per cent for all cases and from 15 to 58.3 per cent for carcinoma in stage 2, according to different authors.

*Operations were done at the Mayo Clinic, but postoperative irradiation mostly by radiologists throughout the country. The irradiation, therefore, is not likely to have been on as high a plane as the operation. (Courtesy, J. A. M. A., Feb. 19, 1938.)

gists confine their postoperative irradiation to the field of operation and axillary and supraclavicular regions. Other radiologists give prophylactic irradiation to the lungs, mediastinum and vertebral column.

A Gunsett follows radical mastectomy by surface mould radium to the axilla, radium needle implantation in the internal mammary lymph drainage region, and x-rays by a protracted divided dosage technique to the tumor bed, supraclavicular fossa, thorax and spinal column.

The value of irradiation in the treatment of carcinoma of the breast¹⁴ can be incontrovertibly demonstrated by the results obtained with recurrent carcinoma, in which there can be no question as to the diagnosis or as to the ultimate outcome if the patient is untreated. The authors have treated 491 patients with postoperative recurrence. Of those who had local recurrence, 39.7 per cent were well 5 years. Of those who had axillary

or supraclavicular recurrence, 23.3 per cent were well 5 years. Of those with distant metastases, 5.1 per cent were symptom free in 5 years, and 18.5 per cent of all the patients with recurrence and metastasis, regardless of the location, were alive and symptom free in 5 years.

Theoretical and Biologic Evidence Favoring Preoperative Irradiation

It is well known that the grade of malignancy has much to do with the prognosis following operation for carcinoma of the breast. The grade of malignancy can be determined only by microscopic examination of the whole breast after removal. Often a carcinoma apparently of Grades 1 or 2 will be found on careful examination to contain some of the more malignant cells of Grades 3 and 4. While Grades 3 and 4 lead to early and extensive metastases, it is also true that they are more sensitive to radiation than are Grades 1 and 2.

TABLE II

RECENT COMPARATIVE STATISTICS FROM VARIOUS CLINICS AS COLLECTED FROM THE LITERATURE

Author	Operation Alone, Percentage Living 5 Years			Operation and Irradiation, Percentage Living 5 Years		
	No of Patients	Stage 2	All Patients Operated On	No of Patients	Stage 2	All Patients Operated On
Lane-Clayton, Janet E Report on the Late Results of Opera- tion for Cancer of the Breast, London, His Majesty's Stat Off, 1928 . . .	2000	24.7 25 0				
Hutchinson			28 1		41.0	40.9
Dawson and Tod .	5615		34 3	1785		44 4
Hintze	4952		28 4	2822		37 9

This group represents cross section statistics collected by various authors from large clinics in various parts of the world. Even this collection shows a gain of approximately 25 per cent in the results of postoperative irradiation and operation as compared with operation alone. (Courtesy, Journal American Medical Assoc, Feb 19, 1938.)

Harrington of the Mayo Clinic has reported that in a large series of cases 91.4 per cent of the group having invasion of the lymph nodes had cancer of Grades 3 and 4. These highly malignant cells are rendered less malignant by even moderate dosage of x-rays. The authors use 900 r delivered to the tumor. Such partially devitalized cells should be less liable to survive implantation as emboli through the blood stream or lymph stream during the manipulations of surgical removal of the breast. The devitalizing effect on the more malignant cancer cells surely occurs immediately, even though it cannot be demonstrated microscopically. Therefore, there is no advantage from this standpoint in prolonging the interval before operation. The preoperative treatment recommended by the authors can usually be given in about 2 weeks so the patient can be operated on in the third week. There is therefore no great delay in the operation. The irradiation moreover does not interfere with the technical procedures during the operation.

Biological experiments by Murphy and Russ and Scott indicate that, in addition to the effect of irradiation on the malignant cells, there is an effect on normal tissue which is detrimental to implantation of carcinoma. Russ and Scott utilized rats in their experiments. They exposed to irradiation 2 opposite quadrants of the outer two-thirds of a circle of skin, protecting the central area of the circle and the other 2 quadrants. They then implanted malignant disease in the unexposed center. In all instances the tumor tissue grew by preference into the unirradiated areas. This effect was evident even when as little as 50 per cent of an erythema dose was used and was also effectual when the irradiation was given several days before the implantation.

Theoretical and Biological Considerations for Postoperative Irradiation

Local postoperative treatment is intended: (1) To destroy any malignant cells that may have been transplanted during operation; (2) to destroy any

microscopic remnant of cancerous tissue which the surgeon may have missed, and (3) to render the normal tissue more resistant to cancerous growth. Definite evidence of implantation is furnished by the rare observance of stitch hole recurrences. Other more frequent implantations probably occur under the skin flap. The authors believe that remnants of cancerous tissue are rendered more malignant and also more radiosensitive by the congestion following the traumatism of the operation. Statistics are presented to show improvement when postoperative irradiation is employed.

The authors affirm that, to get the best effect, the postoperative treatment should be started as soon as the patient's general condition and circumstances will permit, usually within 10 days or 2 weeks, even though the wound is not entirely healed. The postoperative irradiation does not interfere with the healing of the wound.

Ovarian Sterilization as a Preoperative or a Postoperative Prophylactic Measure

It is well known that cancer of the breast is more malignant in young women. Also, it grows more rapidly during pregnancy. Experiments on animals indicate that the ovarian hormones stimulate the production of cancer of the mammary glands in animals that have any susceptibility. On these grounds the authors recommend the ovarian sterilization of all women who have carcinoma of the breast if they are still in the menstrual time of life. Some writers have recommended ovarian sterilization of older women also but other good authorities believe such treatment can have no value after the menopause.

Technic—The authors discuss the technic used by other workers and describe their own.

"Short preoperative treatment is used when the cancer is still clearly in an operable stage but is no longer confined to the breast. The object is to devitalize the more malignant type of cells with moderate dosage without causing undue delay or interference with the operation itself. Ordinarily we aim to finish this preoperative treatment in approximately 2 weeks and to give approximately 900 r through each side of the breast and through the axillary and supraclavicular region. The cross-fire value of this will equal approximately 900 r in the diseased area. For all this treatment we utilize 200 kv, 50 cm distance and 0.5 mm of copper filtration. For portals we utilize the space from the parasternal line to the nipple line, turning the patient on the side and irradiating tangentially, so that the rays will include the chest wall but not penetrate the lungs. A similar tangential dose is given through the mammary area externally, extending from the midaxillary line to the nipple line, also tangentially, avoiding penetration of the lung but including the chest wall. An axillary portal occupies the space between the posterior and the anterior axillary folds, and the rays are directed upward and inward so as to irradiate the axilla, the coracoid or infraclavicular region and the deeper portions of the supraclavicular area; tangential rays are again utilized and the chest walls and the upper mediastinum included. A portal is then utilized, including the supraclavicular region and the coracoid region, and the rays carried from the lower border of the axillary fold upward and inward to the sternoclavicular junction, in stouter persons, a similar portal is utilized through the posterior axillary field, the same general principles being carried out. This should give a rather even distribution of irradiation and should give approximately

an erythema dose value into all of these tissues. This amount of irradiation is intended to be supplemented by postoperative irradiation."

Technic of Postoperative Irradiation—"We generally begin postoperative treatment through a portal occupying the supraclavicular and coracoid region, outlined approximately similar to the one utilized in the preoperative treatment, and for a second portal of entry we usually use the posterior axilla, with the arm thrown over to the opposite shoulder and the rays directed into the axilla, into the deeper part of the supraclavicular region and toward the upper part of the mediastinum. Generally the arm cannot be abducted sufficiently to get a portal of entry into the axilla itself after the operation. As a third field we utilize a large area extending from the lower border of the coracoid and supraclavicular portal to the level of the epigastrium and extending from the right border of the sternum to the left anterior axillary fold. Because of the large area involved, because of the lung and the heart underneath and because irradiation of this area is apt to give rise to radiation sickness, we give relatively smaller doses over this field.

"We utilize for postoperative treatment over this portal the so-called low voltage technic, using 135 kv, 2 mm of aluminum filtration and 50 cm distance. Generally we can give only about 200 or 300 r in each application, sometimes less, but we aim to deliver into this area a total of approximately 1800 to 2400 r, counting both preoperative and postoperative treatment. The treatment is given according to the 'saturation technic,' and we should not exceed a full erythema dose at any time. We aim to deliver into the axilla, coracoid and supraclavicular region approximately 1800 to 2400 r. This will bring about

a definite erythema, but we have not found that it interferes with the healing of the wound or the convalescence of the patient. We believe that treatment should begin about 2 weeks after operation, while the congestion is present and while any cells that have been implanted or transferred are not yet completely adopted to the tissues of the host and while the cancer cell is more radiosensitive than it would be at a later date."

Results of Treatment—It is difficult to estimate the results of treatment because of the difficulties in classification. Until some institution can have a large group of patients carefully studied and classified before operation, operated on by a standard technic, by equally skillful surgeons and then treated by equally skillful radiologists with a standard technic, and then wait until 5 or 10 years to estimate results, it will be difficult to draw conclusions not open to criticism.

"The average number of persons with carcinoma in Stage 2 who survived when treated by operation alone, for a group of the best surgical clinics, is 28 per cent, while the general average for postoperative irradiation is 40 per cent. Our results with postoperative irradiation of carcinoma in Stage 2 show 52 per cent, and when the cases in which preoperative irradiation was used are added it is 57 per cent."

Operable Cancer of the Breast Treated by a Combination of Preoperative Irradiation and Radical Mastectomy¹⁵

Study of Tissue Dosage and Radiation Effect—Soon after the beginning of this work it became evident to the authors that there is a wide variation in the radiation response of breast tumors of apparently the same clinical type. At operation it was noted in a few cases that although the tumor had completely

disappeared clinically, fully viable cancer cells were identified microscopically in the region of the former tumor, especially in the axillary tissues.

The data are tabulated to show the relationship between radiation effect and tissue dosage and are then summarized as follows:

"A series of 201 cases of primary operable mammary cancer were subjected to preoperative irradiation of varying amounts. One hundred and thirty-eight cases were treated by the 200 kv. x-rays, and 63 cases were treated by the 4 Gm. radium element pack. After approximately 8 to 10 weeks following completion of the preoperative irradiation a radical mastectomy was performed. The tissues were then subjected to meticulous pathological study.

"Before treatment was initiated, careful measurements had been made relating to the exact tumor size, thickness, depth, and position in the breast. With all the physical factors of radiation treatment at hand, a study was then made, correlating the tumor dose (T. E. D.) with the resultant radiation effect in the tumor.

"Differing radiation effects are grouped according to a scale of microscopic changes. In both the series treated with x-rays and that treated by the radium pack, certain facts are apparent.

"1. The clinical impression as to the residual tumor can be fairly well relied on (71 per cent for x-ray cases and 75 per cent for radium pack cases) to express the radiation effect obtained.

"2. The larger the minimum tissue dose delivered to the tumor, the more likely is a profound radiation effect to be obtained.

"3. It is necessary to deliver by x-rays at least 6 threshold skin doses within 3 weeks, and with radium almost 3 threshold doses within 6 days to the deepest

portion of the tumor, if the maximum radiation effects are to be obtained in 70 per cent and 56 per cent, respectively.

"4. There is a definite relationship between the size of the tumor mass and the radiation effect obtained.

"5. The chance of obtaining a high radiation effect decreases as the size of the tumor increases.

"6. Since tumors vary enormously in size, as well as in the amount of overlying tissue, it is evident that from the same beam of irradiation, very different doses may be delivered to the most deep-lying tumor cells. The inadequacy of expressing radiation dosage as a certain number of roentgens, or of milligram-hours per port, is evident.

"7. The age of the patient and the differences in interval between completion of irradiation and operation had no apparent influence on the radiation effect observed in the tumor in this series of cases."

Postoperative Roentgen Therapy in Cancer of the Breast¹⁶

In this series the author has complete data on 119 patients followed for 5 years, relative to the first site of recurrence, following operation for cancer of the breast. It is of special interest that recurrence in the axillary region was confined to the cases in which the pectoralis minor had been left in place. It is stated that even with the most meticulous and thorough surgery the incidence of local recurrence without roentgenotherapy will remain around 30 per cent.

Sites of First Recurrence in 119 cases

Local	46
Other Breast	7
Supraclavicular	6
Chest . .	27
Abdomen . . .	14
Osseous	19

Conservative radiologists believe that postoperative irradiation has some value in the treatment of cancer of the breast. Statistics of series of cases showing the percentage of 5-year cures must of necessity deal with the roentgenotherapy of several years ago. The present attitude of the radiologist is that the therapy of that period is archaic. We are told that the present treatment of 3 to 4 weeks of fractional doses with a summation of 7000 to 8000 r is the only proper method. To a surgeon, it seems to indicate a lack of faith on the part of the radiologists in the results that were obtained 5 or 6 years ago. Yet, at that time they were most enthusiastic. It had 1 unfortunate effect upon many surgeons, making them content with inadequate surgery because they thought that irradiation would prevent further trouble.

At present, irradiation is given at the most to the breast area and the regional nodes. A few also irradiate the mediastinum. But even if the conclusions of the most enthusiastic roentgenologists are accepted and treatment is instituted both before and after surgery, or confined solely to irradiation, what are we to do regarding the treatment of cancer that appears elsewhere? It will be noted, in the series of 119 cases in which the first site of recurrence was reported, that over one-half of recurrences were found outside the field of irradiation. Shall we suggest in the future that more fields be irradiated, Shall we include the lungs, the other breast, the vertebrae, the pelvis, the abdomen? Such a course presents many serious difficulties. Is it possible or feasible? Or should we rest content with local surgery and roentgenotherapy?

The author presents statistics from his own work and from several other well-known hospitals and then draws the following conclusions:

"We believe that the Halsted type of operation is indicated except in the matter of skin removal. We have been content to remove a minimum width of 5 inches of skin in early cases with small tumors, to be followed by the wide subcutaneous dissection as advocated by Sampson Handley. Except in small breasts, we are usually able to effect a plastic closure of the skin. When the tumor is large, more skin must be removed followed by immediate Thiersch skin grafting. Our percentage of local recurrence is high, but no higher than those given in the reports from Johns Hopkins Hospital, where the typical Halsted Operation is performed.

"In cases with known sites of recurrence, in which the Halsted-Handley operation had been performed, there were no axillary recurrences. In 69 cases with known sites of recurrence, in which the pectoralis minor was allowed to remain, there were 6 local axillary recurrences.

"Surgery gives a 5-year prognosis of freedom from recurrence that varies with the age of the patient, the type of cancer, and the stage of the disease.

"In our cases without axillary metastasis, roentgenotherapy has unquestionably given a 10 per cent increase in the prognosis of 5-year freedom from disease.

"It is true that this report is a disappointment to us, in that our percentage results are not as good as those reported by the writer in 1927. We had hoped to show improvement with the added routine use of the roentgenotherapy then in vogue. Our only possible explanation may be that our pathologic diagnostic ability is better, and that our cases are more carefully studied and followed up.

"In the hope of improvement, during the past 3 years, we have changed our method to the fractional dose treatment. With this improved method, it is hoped

that the incidence of local recurrences may be reduced and their appearance delayed. Still a real problem is that of regional and distant metastases that are present at the time of operation, although unrecognized. An encouraging approach to this has been made in the sterilization of the patient. I am inclined to doubt the advisability of treating other endocrine glands "

BENIGN HYPERTROPHY OF THE PROSTATE

Radium and Roentgen Irradiation¹⁷—Prostatic hypertrophy does not predispose to cancer. It is dangerous solely because it leads to obstruction to urinary flow with subsequent effects on the urinary bladder and kidneys. The differentiation between prostatic hypertrophy and cancer taxes the skill of a trained urologist. The radiologist should not treat these cases unless he has the co-operation of a competent urologist.

In treating prostatic hypertrophy, the author has used telerradium therapy in dosages varying from 10 Gm.-hr. through 1 perineal portal to 60 Gm.-hr. through 3 portals. In the cases treated in this manner, 50 per cent had symptomatic relief with reduction in size of tumor, reduction in residual urine and improvement in functional renal tests. The beneficial effects of the treatment may last for only a few years. Some patients required only a small amount of treatment while other patients required extensive treatment in order to show improvement.

CANCER OF THE PROSTATE

In treating cancer of the prostate, the author has employed much larger dosages than he used in simple hypertrophy. A telerradium apparatus at 7.5 to 10 cm

distance delivered, through multiple portals, a total of 100 to 300 Gm.-hr. spread out over a period of 2 weeks to 3 months. In some cases radium was employed by intravesical, intrarectal or interstitial implantation. In other cases, x-ray therapy was given in addition.

Conclusions—1. Improvement in absolute cure percentages in the future will depend on discovering and treating the disease in its incipency and early stages.

2. Prostatic cancers vary greatly in their sensitivity to radiation and in their degree of malignancy.

3. Intravesical and intrarectal treatments are, from the physical standpoint of dosage, inadequate when employed alone, and limit the use of better methods when combined with them. This is particularly true from the viewpoint of palliation. Even with objective improvements, symptomatically the patients are often more uncomfortable.

4. Cross firing with radium at a distance, or, as we now feel is equally as good, with roentgen rays, is the most valuable palliative method at our disposal and may actually bring about cure in a few of the cases beyond any possibility of operative treatment.

5. Radium implantations should be reserved for use in cases presenting a possibility of cure. This excludes the metastatic cases and the huge growths.

6. In all cases where either operation or implantation is considered, such procedure should be preceded by an adequate irradiation, such as is now used in mammary cancer, and it should be considered as a postoperative and postimplantation procedure in some cases.

7. Obstruction, necessitating catheterization, and not promptly relieved by irradiation, should be treated by electro-surgical resection as a preliminary to further irradiation.

8. Metastatic cases should be treated, as marked palliation can often be secured, relief of pain being the outstanding feature

PALLIATION OF CANCER IN GYNECOLOGY¹⁸

The cancer specialist reports his so-called "5 and 10 year cures," whether accomplished by destructive surgery or by the use of physical agents, but says little about the patient's discomfort, disfigurement, or obnoxious condition following attempted cure. The literature of cancer treatment contains relatively little about the use of proper judgment as to when not to treat cancer patients. Lee has shown that in advanced cancer of the breast the curve of life for treated patients is almost identical with Daland's curve of life for patients not receiving treatment. The urge to do something for the patient expends itself too often in merely doing something to her.

From the record it is evident that, in spite of pleas for early diagnosis, the majority of patients presenting themselves to cancer institutions have advanced disease. The treatment of advanced cancer is purely the palliative attempt to give relief from symptoms. The symptoms requiring palliative relief are the cardinal symptoms of cancer. Pain, hemorrhage and obnoxious discharge. All are late symptoms and mean advancement of the disease.

Pain

Pain is caused by direct involvement of sensory nerves or by pressure on them. In a lesser degree it may be discomfort from the bulk or weight of a tumor with resultant embarrassment of respiration, or urinary or intestinal functions. Palliative relief of pressure discomfort may be achieved by the removal of bulk, as in vulvar or ovarian tumors, or by frequent

paracentesis for ascites. Many drugs give temporary relief for cancer pain, but all require substitutions in a relatively short time. Compounds of *salicylates* seem to be the most satisfactory in the first stages of pain. As these become inadequate, *codeine*, starting with small doses, is the most valuable narcotic. The use of morphine in the early stages of cancer pain is one of the mistakes most often encountered. Patients rapidly acquire a tolerance for large doses until very soon even huge doses fail to give relief. Morphine should be reserved for the last few weeks of the terminal stage. The present-day substitutes for morphine have the same faults and in most instances fail to equal the efficiency of morphine. *Alcohol injections, chor-dotomy*, and *hypogastric sympathectomy*, with their admitted limitations, all have their place in the relief of terminal pain.

Hemorrhage

Hemorrhage, always a manifestation of friability of tissue and blood vessel involvement, can often be controlled by physical agents such as the actual cautery. Irradiation also has its place in the control of hemorrhage. Patients with low hemoglobin or red cell count should be transfused repeatedly, as anemic patients tolerate poorly either irradiation or postcautery slough. The low blood volume of cachectic patients often gives a misleading red blood cell count.

Obnoxious Discharge

Obnoxious discharge, evidence of necrosis of tissue and invasion of lymphatics, requires relief. The sloughing, fungating, bulky tumors of the vulva and cervix can be greatly reduced with the cautery. The lesions can be cleaned to an astonishing degree by the use of pressure sprays of *Dakin's solution, peroxide*, or *sodium perborate*. *External irradiation* by

the divided dose method in cases of carcinoma of the cervix removes much of the infected sloughing lesion. After this it is much easier to apply radium. Some patients considered hopeless obtain palliative relief by the external irradiation alone.

Pyometra

Pyometra is most commonly found with carcinoma of the corpus, but also occurs in carcinoma of the cervix especially in advanced cases. More than one-third (39 per cent) of patients with pyometra have retroverted uteri and the condition is probably the result of the uterine postural state. Probably an earlier correction of the retroversion would favor less palliation in the later stages.

Fistulae

The author has published¹⁹ a review of 2852 cases of carcinoma of the cervix, treated at Memorial Hospital between 1916 and 1932. He showed that vaginal fistula is primarily a manifestation of advancement of the disease, for its incidence was twice as high in untreated cases as in irradiated cases. Infection was found to be an important factor in fistula formation and the cleaning up of infected lesions by preliminary external x-ray therapy should help to prevent formation of vaginal fistulae. Untreated patients with vaginal fistulae should be rejected as too far advanced for beneficial therapy. Any therapy will only add to their discomfort. The repair of any fistula appearing after radiation therapy should not be attempted until the patient has remained free from disease for 5 years.

PRIMARY AND RECURRENT CARCINOMA OF THE UTERINE CERVIX²⁰

Treatment with Interstitial Radiation—The authors state that the treat-

ment of cancer of the cervix should not be given in a routine manner, as no single method is suitable for all individuals. They recommend starting the treatment by means of external radiation for the purpose of reducing infection so that the local reaction to subsequent radium therapy will be lessened. An initial treatment by x-rays also facilitates radium treatment by causing reduction in the size of the lesion.

In the treatment of carcinoma of the cervix it is essential that a large dose be given to the parametrium without over-radiating normal structures in other regions. A 6-field technic (2 on the anterior surface, 2 on the posterior, and 1 on each lateral aspect of the pelvis) was found to deliver the greatest amount of radiation to the parametrium without too great a percentage of the total dose falling upon the bladder and rectum.

There is general agreement that an intrauterine tandem containing radium will not control neoplasms located more than 3 or 4 cm from the cervical canal. Various intravaginal applicators have been devised to increase the radius of effect of radium.

The distribution of radiation for different methods of applying radium to the cervix has been shown diagrammatically by the author in a previous publication. These diagrams showed that radium alone is inadequate for most patients. They show also that a greater number of sources of radium distributed more widely throughout the uterus and vagina wall, for specified doses, increase the minimum amount of radiation reaching the tumor, and decrease the risk of over-radiating some regions. It is obvious that normal structures must be protected from doses that will result in permanent damage, but it should be noted also that the minimum dose is even more important than the maximum amount of radiation

delivered to a given volume of tissue. If the dose reaching some parts of the tumor is less than the amount required for producing a lethal effect upon the disease, that portion of the tumor will recover from the temporary effect of the treatment and then continue to grow.

The most logical means of distributing a greater number of sources of radium more widely throughout the tumor-bearing area is by means of interstitial radiation such as needles, seeds, etc. Several authors both here and abroad have reported the use of interstitial radiation. Many gynecologists have been reluctant to try it because of the fear of introducing infection into the tumor by the insertion of needles and seeds. Pitts and Waterman have reported their results in a large series of cases and did not find that infection or other complications were frequent following interstitial implantations. In most patients, radium alone is inadequate for delivering a lethal dose to the entire tumor-bearing region. External radiation is essential in the attempt to treat adequately the disease located in the outlying tumor-bearing areas, and in the deep lymphatics

There is evidence that for specified methods of treatment control of the disease in carcinoma of the cervix requires a minimum of from 6 to 8 threshold doses. Frazell showed, by calculating tumor doses in relation to 5-year survivals, that relatively few patients were cured when some portions of the tumor received less than 3 threshold doses. The percentage of survivals was found to increase among patients who had received greater amounts of radiation.

The author has prepared charts for various strengths and lengths of radium applicators, laid out on celluloid (old x-ray film). These charts, in the form of circles, show to what distances from the various radium applicators 1 and 2 thresh-

old doses will be delivered. Similar circular charts show the distances from larger radium applicators, used in intra-uterine treatments, at which 1, 4 and 7 threshold doses will be delivered at 1000 mg.-hr. and 3000 mg.-hr. The author explains the use of these charts for quick estimation of the distribution of radium required for proper treatment of various sized tumors. He then shows roentgenograms of the radium applicators in position during the treatment of cases, the distribution of applicators having been worked out by the author's method.

The author's charts or isodose curves have proved to be useful aids in teaching the principles of interstitial radiation. They present a fairly rapid method for determining the amounts of radiation required for delivering a predetermined tissue dose considered adequate for a given lesion. Furthermore, use of the charts necessitates a careful planning of radiation that insures individualization of treatment.

Survey of Treatment and Results in 1491 Cases²¹—Radium therapy has been employed at the Mayo Clinic in the treatment of carcinoma of the uterine cervix for the past 22 years, and today ranks as one of the most effective methods of treating this dread disease.

The importance of suitable classification of the lesions cannot be overestimated. From the standpoint of radium therapy, the extent of the malignant process when the patient presents herself for treatment should be the guiding factor in such a classification. Careful vaginal and rectal bimanual abdominal palpation with the patient in the dorsal position on a standard office examining table, and inspection of the vaginal cavity using some type of direct light and a Sims speculum with the patient in the knee-chest position, are the most satisfactory procedures to facilitate diagnosis and to

TABLE III

CARCINOMA OF UTERINE CERVIX (1915-1929) CLASSIFICATION ACCORDING TO TYPE OF LESION AND STAGE OF INVOLVEMENT

Type of Lesion	Stage				Patients	Percentage
	I	II	III	IV		
Early	13				13	0.9
Borderline		85			85	5.7
Inoperable			825	156	981	65.8
Modified	4	28	297	83	412	27.6
Total	17	113	1122	239	1491	100
Per cent	1.1	7.6	75.3	16.0		

(Courtesy, American Journal of Roentgenology, July, 1938)

determine the extent of involvement. To determine the presence of metastatic lesions, the inguinal and supraclavicular lymph nodes should be carefully palpated. The most valuable single laboratory procedure is roentgenographic examination of the thorax for evidence of metastasis to the lungs. In the presence of severe pain, and especially if the involvement tends to cripple the patient, a roentgenogram of the area may reveal metastasis to bony structures.

The most common clinical sign of carcinoma of the cervix is extramenstrual bleeding. In the 13 cases with early lesions there were 12 (92.3 per cent) with bleeding. In 85 cases with borderline lesions there were 81 (95.3 per cent) with bleeding. In 981 cases with inoperable lesions there were 936 (95.4 per cent) with bleeding. In the total of 1491 cases there were 1413 (94.8 per cent) with bleeding.

Other tables show the number of patients in different age groups, grade of malignancy and hospital mortality.

Treatment with radium was by the intensive, broken-dose method, employing in most cases the universal silver tube containing 50 mg. of radium sulfate (element) or 50 mc. of radon. The time of treatment and the interval between

applications are very important. Further details regarding exact technic of treatment are given in the next paper by the same authors. The filtration employed consisted of 0.5 mm. of silver and 1.0 mm. of brass. The vaginal applicator contained an additional 2 mm. of lead and 1 cm. of Para rubber.

Treatments, with very few exceptions, were given with the patient in the knee-chest position. In this way the applicator could be effectively placed and the results of previous applications estimated from time to time during the course of treatment, thus facilitating individual therapy. When necessary, the vaginal cavity was

TABLE IV

CARCINOMA OF UTERINE CERVIX (1915-1929)
TYPE OF MALIGNANCY

	Cases	Per Cent
Epithelioma	880	59.0
Adenocarcinoma	53	3.5
Carcinoma (not specified)	550	36.9
Epithelioma and Adenocarcinoma	7	0.5
Endothelioma	1	0.1
Total	1491	100

(Courtesy, American Journal of Roentgenology, July, 1938)

TABLE V
CARCINOMA OF UTERINE CERVIX (1915-1929) GRADE OF MALIGNANCY

Type of Lesion	Grade				Not Graded	Patients	Per Cent
	1	2	3	4			
Early			7	1	5	13	0.9
Borderline		9	27	18	31	85	5.7
Inoperable	4	95	303	246	333	981	65.8
Modified	1	31	70	71	239	412	27.6
Total	5	135	407	336	608	1491	100
Per Cent	0.3	9.1	27.3	22.5	40.8		
Per Cent of Graded Cases	16.0		84.0				

(Courtesy, American Journal of Roentgenology, July, 1938)

carefully cleansed and other measures were employed to combat the usual secondary infection. Normal tissue was protected through accurate placement of the applicator and vaginal packing to maintain the applicator in position and to keep the adjacent vaginal walls away from the center of treatment. As a rule all patients received supplemental roentgen irradiation, with rays generated at 200 kv, following the course of radium therapy.

Patients with small lesions which are limited to the cervix or show only slight extension and which are adequately treated, show the highest percentage survival rate. Patients with moderately large or extensive lesions have a definite chance of recovery, although the percentage survival rate is definitely lower.

Summary and Conclusions — We feel that the intensive broken-dose method of radium therapy, followed by a course of roentgen treatment after thorough study and planning of each individual case, offers the best results in this unfortunate group of cases. In this large series, extending over a period of 15 years, although the great majority of patients (91 per cent) were in an advanced stage of the disease, of the entire number 26.8 per cent lived 5 or more years, apparently well following treatment. The possibilities of this form of treatment for

early and borderline lesions can be appreciated when it is noted that 69.2 per cent of patients with lesions in Stage 1 were well at the end of 5 years.

This form of treatment, of course, requires considerable individual care and experience; it also requires co-operation between patient and physician. The proper handling of emergencies as they arise during a course of treatment is an important factor. That there is little risk in the treatment is attested by the fact that the hospital death rate for the entire series was only 1 per cent, the mortality occurring in the group with advanced lesions. There were no deaths at all during treatment in the early or borderline groups.

RADIOSENSITIVITY OF MALIGNANT NEOPLASMS OF THE UTERINE CERVIX²²

Carcinoma of the uterine cervix is radiosensitive. The lesion was one of the first to be found susceptible of being destroyed by radium and roentgen rays. The radiosensitivity of carcinoma of the cervix is relative and is dependent on various factors. Some of these factors can be evaluated. Ewing said: "The general condition of the patient determines the result of radiation, regardless

of nearly all other factors. In fresh subjects in good general health, without anemia or cachexia, the results of radiation are usually prompt and definite, whereas in anemic and cachectic subjects with poor circulation, tumors may fail entirely to respond."

tion can be determined by frequent observations during the course of treatment. The duration of this response can be determined by the number of 3-year or 5-year cures in a group of cases. The data presented in this paper were obtained from the daily experience of the

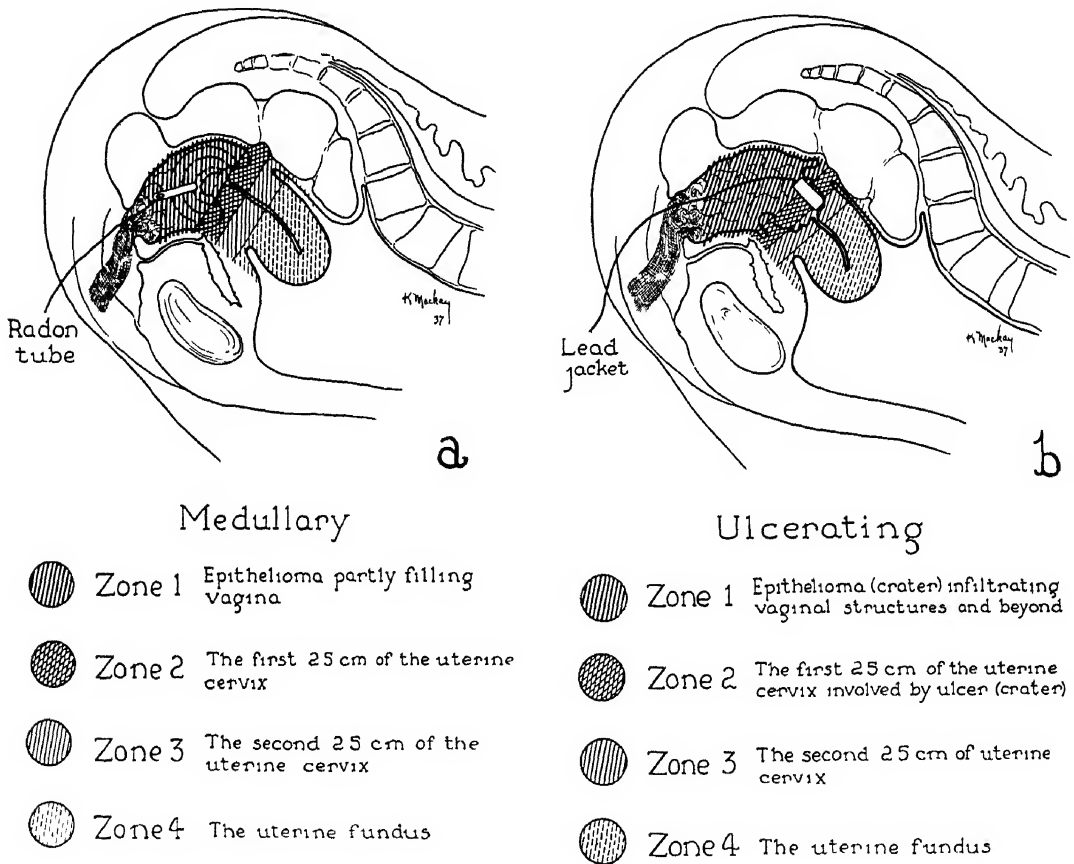


Fig. 20 Treatment of (a) medullary type, and (b) infiltrating type of uterine carcinoma. Patient in knee-chest position and applicator in place (Bowing & Fricke J A M A, Nov 19, 1938)

Some of these factors can be recognized grossly while others are recognized microscopically. The former lend themselves rather well to recognition and discussion while the latter may be studied only by examination of material which is removed at operation or for biopsy, and by post-mortem examination of specimens by skilled pathologists.

The capacity of a given malignant lesion of the cervix to respond to irradiation

can be determined by frequent observations during the course of treatment. The duration of this response can be determined by the number of 3-year or 5-year cures in a group of cases. The data presented in this paper were obtained from the daily experience of the

authors and from the 3-year results obtained in a group of 1491 cases in which treatment was given in the years 1915 to 1929, inclusive.

As a rule, the diagnosis can be made from the chief complaint, history, bimanual pelvic examination and inspection of the vaginal cavity, preferably with the patient in the knee-chest position.

In the early years covered by this report, biopsy was done in a limited num-

ber of cases but in the latter years it was done as a routine.

Malignant neoplasms of the uterine cervix consist chiefly of squamous cell epitheliomas, which have a dominant tendency toward the higher grades of malignancy. The remaining small group

Stage 1—Primary lesion limited to cervix.

Stage 2—Primary lesion has extended beyond the original site but the uterus is movable.

Stage 3—Primary lesion has extended farther than Stage 2; uterus is movable.

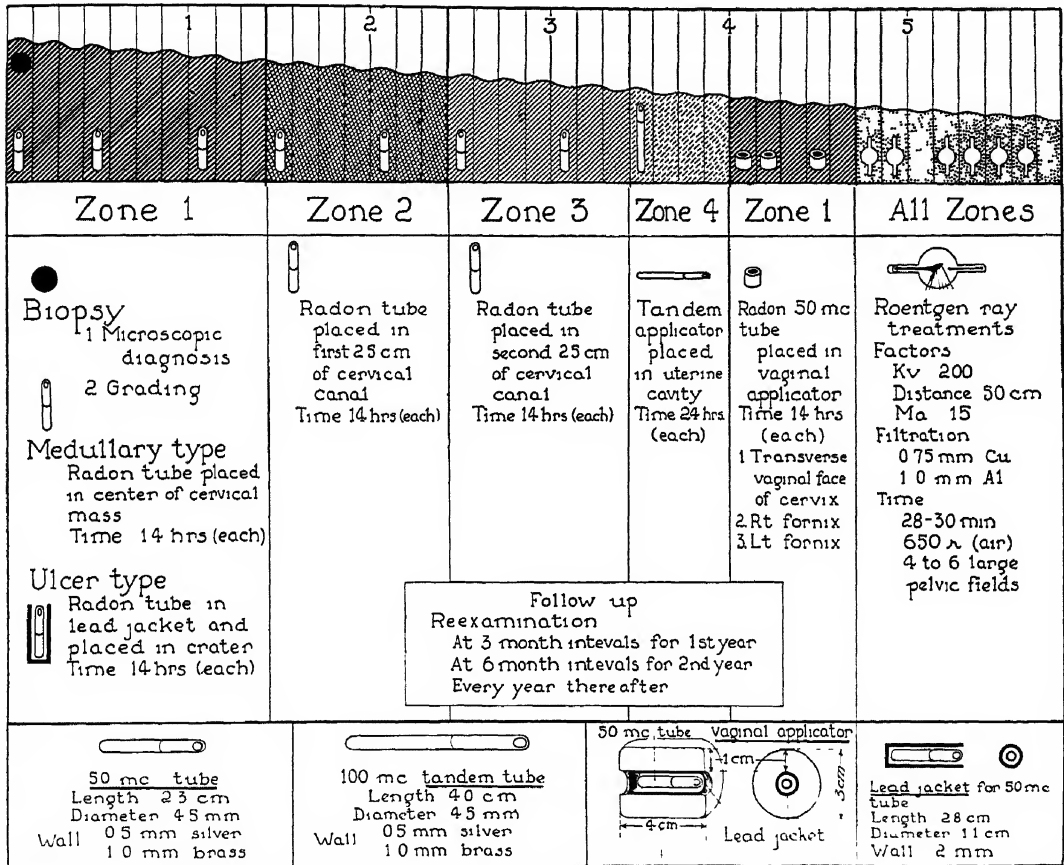


Fig 21—Schedule of radium treatment for the average stage 3 involvement in a case of carcinoma of the uterine cervix. Each of the Arabic numerals across the top of the drawing indicates the end of 1 week of treatment. The vertical line which is intercepted by each Arabic numeral, and every other similar vertical line, indicates the end of 1 day. The wavy line which descends from left to right indicates the decreasing infiltration and the general improvement of the patient's condition as treatment progresses. Directions for a complete treatment can be obtained by reading the chart from left to right. (Bowing & Fricke, J. A. M. A., Nov. 19, 1938.)

is made up of adenocarcinomas and a few mixed lesions which contain both of these malignant cellular elements.

From the standpoint of radium therapy, it is important to classify the lesions according to the extent of the primary and secondary involvement. The following classification has proved satisfactory.

Stage 4—"Frozen pelvis" with extensive pelvic involvement and probable local and distant metastases.

The term "modified" is used to describe the stage of involvement in cases in which some type of therapeutic procedure had been employed before the patient came for radium therapy.

TABLE VI

RESULTS ACCORDING TO THE TYPE OF RADIUM TREATMENT EMPLOYED

Classification of Radium Treatment	Patients Treated	Patients Traced	Patients Who Lived 3 or More Years After Treatment	
			Number	Per Cent of Those Who Were Traced
Complete	604	565	299	52.9
Limited	807	739	158	21.4
Abandoned	39	33	10	20.3
Total	1450*	1337	467	34.9

*This does not include 41 cases in which roentgen therapy was used alone (Courtesy, Journal American Medical Assoc., Nov. 19, 1938)

The technic used by the authors in the treatment of carcinoma of the cervix by means of radium is called the intensive, multiple or broken-skin-dose technic. The treatment factors, amount of radium, filtration and distance, were constant, while the interval between applications and the time of application were varied to meet the needs of each individual patient. Nearly all patients were placed in the knee-chest position in order to permit careful inspection and the introduction of applicators without trauma. Intervals between treatments are necessary in order to determine the radiosensitivity of the treated lesion. In cases in which such complications as tumor necrosis, local cellulitis, ulceration of the vaginal walls indicative of potential fistulas, or pyometritis are present the intervals permit measures to be taken to combat these complications.

Further details of technic are shown in Figs. 20 and 21.

The outline of treatment is suitable for the average patient with a Stage 3 involvement.

The radium therapy was followed by a course of high voltage (200 kv.) roentgen therapy in 1450 cases out of the total of 1491 cases. In the remaining 41 cases roentgen therapy was the only treatment used.

If radium treatment was carried out according to the above outline, it was classed as "complete." If owing to the extent of local or pelvic involvement only part of the treatment could be carried out according to the outline it was classed as "limited." If it became necessary to stop treatment before completion of the outlined course, it was classed as "abandoned." Table I shows that 52.9 per cent of patients receiving a "complete" course of treatment lived 3 years, 21.4 per cent of patients receiving "limited" treatment lived 3 years, 20.3 per cent of patients whose treatment was "abandoned" lived 3 years.

This result is all the more significant because in more than 90 per cent of the 1491 cases the involvement was extensive enough to be classed in Stage 3 and Stage 4, as shown in Table VII.

The authors have not presented data to confirm their statements regarding the immediate results following radium therapy. They state, however, that all treated patients were benefited, vaginal bleeding stopped and in many cases the relief of pain was prompt. The degree and duration of this improvement depended upon the extent of malignant involvement and the adequacy with which radium therapy was applied.

TABLE VII

RESULTS OF TREATMENT OF CARCINOMA OF THE UTERINE CERVIX WITH IRRADIATION ALONE,
BASED ON STAGE OF LESION

Stage of Lesion	Patients Treated	Patients Traced	Patients Who Lived 3 or More Years After Treatment	
			Number	Per Cent of Those Who Were Traced
Stage 1	13	13	13	92.3
Stage 2	85	81	57	70.4
Stage 3	825	760	292	38.4
Stage 4	156	142	18	12.7
Modified Stage 1	4	4	4	100.0
Modified Stage 2	28	26	18	69.2
Modified Stage 3	297	271	68	25.1
Modified Stage 4	83	74	4	5.4
Total	1491	1371 (91.9%)	473	34.5

(Courtesy, Journal American Medical Assoc, Nov. 19, 1938)

TABLE VIII

RESULTS OF RADIATION THERAPY ACCORDING TO 5-YEAR PERIODS IN WHICH TREATMENT WAS GIVEN

5-Year Period in Which Treatment Was Given	Patients Treated	Patients Traced	Patients Who Lived 3 or More Years After Treatment	
			Number	Per Cent of Those Who Were Traced
1915 to 1919, inclusive	288	264	38	14.4
1920 to 1924, inclusive	556	522	185	35.4
1925 to 1929, inclusive	647	585	250	42.7
Total	1491	1371 (91.9%)	473	34.5

(Courtesy, Journal American Medical Assoc, Nov. 19, 1938)

The authors have analyzed their results according to grade of malignancy and also to the age of the patients. Their figures show that the young patient with malignant disease has a poorer prognosis than does an older patient.

Table VIII shows how the results improved when heavier treatment was given in later years. The patients treated early in the period 1915 to 1919 received only a limited radium treatment of about 2000 mg.-hr. This was supplemented by low voltage roentgen therapy. While the initial results were favorable, there was

recurrence of activity after several months. The initial treatment was repeated with palliative results. Many patients received several series of treatments.

A careful review of these cases encouraged the authors but it was evident that the technic was deficient as it did not provide proper distribution of the therapeutic rays of radium and the initial dose was too small. The dosage was then increased and after 1920 far better results were obtained, as may be noted by inspection of Table VIII.

At the present time an initial complete treatment is repeated only in rare cases. In such cases the repetition may produce relief that will last for years.

Dr. Henry L. Schmitz, of Chicago, discussed the paper as follows:

"The paper of Drs. Bowing and Fricke concerns the prognosis and course of the disease in relation to the extent of the growth and the general constitutional condition. The study of the clinical extent of the growth called by the writers Stages 1, 2, 3 and 4 either modified or unmodified, would be facilitated if the clinics would agree on the same definitions for each stage. It would then be possible to evaluate the end results of the various forms of treatment of carcinoma of the cervix. The widest differences are found in the definitions of clinical Groups 1, 2 and 3. The difference between clinical Group 1 and clinical Group 2 cases is mobility of the uterus. It is normal in the former if one attaches a forceps to the uterus and it can be displaced down to the entrance of the vagina without causing the patient any distress. In clinical Group 2 the uterus is limited in mobility, though movable, and it cannot be displaced downward unless one uses an appreciable pull. Limited mobility may be due to either an extension of the carcinoma or an inflammatory reaction in the pericervical tissues. It is clear that a patient with an inflammatory loss of mobility of tissues will do better than one with a carcinomatous invasion of the paracervicum. The clinical Group 3 case is characterized by an invasion of either one or both parametria yet mobility of the entire mass is still present. There should be made a distinction between fixation and limited mobility of the tumor. As soon as the carcinoma becomes fixed, a clinical Group 4 carcinoma is present. Presence of local or distant metastases, or invasion of adjacent organs

as bladder, vagina or rectum in the absence of fixation, also stamp such as cancer as belonging to clinical Group 4. Such a clinical grouping of the extent of the growth is very important for the selection of the indicated form of treatment and for the study of the good end results. I do not wish to add to these definitions, as the proper grouping alone will enable one to select the treatment and to prognosticate the results."

INOPERABLE COLLUM CARCINOMA

Results Obtained in Radiation Treatment²³—In his report from Budapest, de Buben has confined himself to inoperable carcinoma of the cervix. Many of the cases of cervical carcinoma are found to be so far advanced that operation cannot be considered and radiation is the only hope left for relief. In fact, in a very small percentage of cases a cure has been effected by radiation even in cases that were far advanced.

Carcinoma of the cervix is characterized by the swiftness with which it invades the neighboring tissues, bladder, rectum, ureter and parametrium. Winter stated that carcinoma of the cervix reaches the limit of operability in 4 to 6 weeks, whereas carcinoma of the body of the uterus remains in an operable condition for months.

The signs and symptoms for carcinoma of the cervix are blood-tinged discharge, hemorrhages, and pain. Pain occurs in the later stages rather than in the early stages. Many patients ignore the early signs, blood-tinged discharge and hemorrhage, and apply for treatment only when the pain becomes severe. Pain usually signifies that the cancerous growth has extended into the surrounding tissues, especially the parametrium. Thus the cancer is in many cases inoperable

when the patients first seek medical advice.

The greatest obstacle to successful irradiation of the uterine cervix is the fact that the normal structures in this region are sensitive to radiation. Radium is employed for local treatment but its dosage must be kept low enough to avoid serious injury to the bladder and rectum. X-rays must, therefore, be used for supplementary treatment to destroy the malignant cells which have spread beyond the immediate neighborhood of the cervical canal.

Local treatment includes radium placed in both cervical canal and vagina. If the cervical canal is obstructed by the neoplasm an applicator must not be forced into the canal. Treatment should be given with radium placed in the vagina and then after an interval of 3 or 4 weeks there may occur enough shrinkage of the cancerous tissues to allow an easy introduction of an applicator into the cervical canal for further treatment.

In using radium in the vaginal vault, a heavy filter, 1 to 2 mm. of platinum or equivalent, should be employed so as to cut down as far as possible the injurious effect on normal tissues, especially the bladder and rectum. Even with this heavy filtration radium tubes should be at least 1 cm. away from the bladder and rectum. This is accomplished by using cork containers and ring pessaries made of rubber.

In using radium in the cervical canal, the filtration should be 1 mm. of platinum or its equivalent. The applicators should be sterile to reduce the possibility of infecting the canal.

The author gives the radium treatment first in the vaginal vault with 2 applicators of 25 mg. each with primary filtration of silver-brass-lead equivalent to 1.5 mm. of platinum. These tubes are left in place 24 to 48 hours, making a dos-

age of 1200 to 2400 mg.-hr. A radium applicator, with 1 mm. of platinum filtration, is then introduced into the cervical canal and left in place long enough to make the total radium dosage 4000 to 6000 mg.-hr. Treatments are repeated after several weeks, varying according to the needs of the individual patients.

To supplement the radium therapy, de Buben uses x-rays delivered through 3 to 6 fields. Three treatments with a total of 1500 r. per field are given. His technical factors are: Valve tube rectification, 190 kv., 5 ma., 0.5 mm. Zn plus 0.5 mm. Al filtration, distance 30 cm.

After irradiation, the progress of the patients is followed by examinations every 6 weeks, later every 3 months and still later every 6 months.

Injuries to the bladder seldom follow radium treatment and even when edema of the base of the bladder does occur it does not last long. Complaints of injury to the rectum are somewhat more common. Even average doses of radium may cause tenesmus, which may be severe enough to affect the general condition of the patient.

Fistula formation is another of the rare sequelae which sometimes occur even with the very best technic which our present knowledge allows.

The author reports the results of the treatment between 1919 and 1929 of 702 cases of inoperable cancer of the cervix. Of these, 658 cases were in Group 3 and 44 cases were in Group 4. Group 3 includes an inoperable condition where the uterus is fixed and the carcinoma has invaded the neighboring tissues. Group 4 is comprised of highly advanced and hopeless cases.

According to Forssell, the absence of symptoms for 1 year after the completion of treatment shows a palliative effect directly resulting from radiation therapy. This he calls primary healing.

In the author's series of 702 cases of inoperable carcinoma of the cervix there were 305 cases (43.1 per cent) of primary healing. The symptoms were absent for

1 year	155 cases
2 years	68 cases
3 years	23 cases
4 years	21 cases
5 years	14 cases
6 years	9 cases
7 years	6 cases
8 years	3 cases
9 years	1 case
10 years	1 case
11 years	2 cases
12 years	2 cases

(Of the 44 hopeless cases belong to Group 4 there were 18 cases which lived for 1 year as a result of some degree of temporary benefit from the radiation therapy.

CANCER OF THE UTERUS²⁴

Costolow has had extensive experience in treating cancer of the uterus. Years ago he learned that his results improved when he used larger doses of x-rays and radium. With radium it proved to be advantageous to increase the filtration so as to cut down the injurious effect on tissues immediately surrounding the radium applicators. His present method is given in his own words:

"Since 1933 in our present technic, a voltage of around a half million is used with the Lauritsen type tube—distance 52 cm., filter 0.6 mm. lead (equivalent 12 mm. or $\frac{1}{2}$ inch copper), effective wave length, 0.05° Angstrom; half value layer, 0.5 mm. lead, in aluminum, half value, 23 mm. aluminum, depth dose, 53 per cent at 10 cm. (in paraffin). Treatment rate is 15 r per minute. Four or 6 pelvic portals are used; 2, 15 by 15 cm. portals anteriorly over the pelvis; 2, 15 by 15 cm. portals posteriorly, and 2 laterally, if 6 portals are used. Daily, 2 portals

receive 150 r units (measured in air); total dosage of from 1600 to 2000 r is given each portal. This produces a definite erythema with desquamation. Diarrhea is complained of in many cases but usually soon disappears if the daily dosage is decreased. In some cases 300 r is given daily, alternating the 4 or 6 portals. With safety, from 10,000 to 12,000 r units may be given over a period of from 5 to 6 weeks. The plan of this treatment should be individualized considerably according to the size of the patients and their ability to withstand the irradiation.

"The primary growth is markedly influenced by the x-ray series. Often, a cauliflower primary growth of a high degree of malignancy will completely disappear after such a series.

"Following the x-ray series, radium applications are commenced immediately, a divided series of vaginal and intrauterine applications being given. In the vaginal application, 2 mm. of gold and 1 mm. of aluminum filter is used, and in the intrauterine application, 1 mm. of gold and 1 mm. of aluminum is used. Previously, we applied a vaginal dosage of from 1200 to 1400 mg.-hr. and an intrauterine dosage of from 900 to 1200 mg.-hr. This was repeated in 1 week and again in 2 weeks. Since the super-voltage x-ray has been used, we have reduced the vaginal vault dosage, but have not eliminated it. Usually, however, most of the radium dosage is given intrauterine. With 1 mm. gold filter, a dosage of from 4000 to 6000 mg.-hr. may be given. This dosage is divided into 1- and 2-week intervals. Many cases which have had the full radium dosage have not shown any bad effects following this heavy irradiation. The fact that the radium follows immediately after the x-ray series is probably the important factor in preventing unduly

delayed reactions, because the tissues in the vaginal vault and cervix have not had time to develop fibrosis and interference with the local circulation, which occurs from 4 to 6 weeks following intensive irradiation.

"Certainly, the intrauterine radium can do no harm to the bladder or rectum, as distance and filtration prevent much irradiation outside of the walls of the uterus. We believe the radium dosage absolutely essential in order to give sufficient irradiation to the uterine canal and cervical glands "

TOXIC GOITER

Value of Irradiation²⁵—Pfahler and Vastine in 1930 reported their results following the irradiation treatment of 235 cases of exophthalmic goiter. There were 6-year cures in 58 per cent of the patients. The criteria of cure were; the absence of toxic symptoms, absence of visible thyroid enlargement, absence of recognizable myocardial change, and diminution in exophthalmos. Besides the patients listed as 6-year cures there were 28 per cent markedly benefited and able to resume their occupations with some restriction of activity. The percentage of cures was no higher in the mild cases than in the more severe cases. The sooner after the onset of symptoms the treatment was begun the better the results.

In a series of 92 patients with toxic adenoma treated by irradiation Pfahler obtained either a cure or marked improvement in 91 per cent. He found that the enlargement in exophthalmic goiter most often disappeared completely following irradiation, but it usually was the last symptom to disappear. Adenomatous goiter was reduced in size but did not disappear completely.

In a later report Pfahler's technic was the following: 130 kv. peak, 5 ma., 8 min. at 30 cm. distance, filtered through a combination filter of copper and aluminum equal to 6 mm. of aluminum. This gave 40 per cent of an erythema dose for the equipment used. Two anterior and 2 posterior fields, each about 5 by 15 cm. to include both the thyroid and thymus glands, were employed. It was necessary to protect the larynx and the remainder of the body. Pfahler gave the series of 4 doses in succession in 1 day, repeating in 3 weeks and then in 4 weeks. Therapy was discontinued as soon as the basal metabolism was reduced to plus 15. The average number of treatments in which a series of 4 fields was given in 1 day was 6.1 for the cured cases, 5.7 for the improved cases; and 3.7 for the unimproved. Pfahler believes that the results obtained by irradiation were equal to those obtained by surgery, with less shock and risk to the patient and without the danger of hypothyroidism and tetany. Pfahler concludes as follows:

"Not surgery, nor irradiation, nor medication can be depended upon to cure all cases and no 1 method is so much superior that we can recommend it to the exclusion of the other 2. Our records show almost exactly as many cases referred by us to surgeons as were referred to us after surgery had failed. It is the general opinion of radiologists that all cases which are not seriously involved by mechanical pressure, or so acute as to make delay of 1 month dangerous, should be treated by irradiation. Irradiation and every valuable method of medication can certainly be employed to advantage. If there is no definite improvement after 2 or 3 months, surgery can still be used. The delay which always precedes operation can be used to advantage in this man-

ner. When irradiation fails, surgery can still be used; when surgery fails, irradiation can be used. Medication and the advice of the internist are of value in all cases, but there will remain a small number in which we all will fail."

Harris reported the results of 7½ years' observation of cases of toxic goiter irradiated at the University of Pennsylvania. During the first part of the period, the technic consisted of 135 kv. peak, 5 mm. aluminum filtration, 4 min., through 4 by 4 inch portals to 4 different areas over the gland. Approximately 125 r were given in this manner and a series was given at 3-week intervals. Later the dosage was increased to 250 r, which were given to the gland through 1 large portal with 135 kv. peak (mechanical rectification) 5 ma., and 30 cm. distance. The output with these factors was 27 r per minute; half-value layer 0.42 mm. copper, and effective wave length 0.23 Å. The portal was 12 by 15 cm. and included the anterior thyroid area and the cervical sympathetics with protection to the larynx. An alternate technic employing higher voltage when low voltage had been ineffective was used occasionally. This was 165 kv. peak (valve tube rectification), 15 ma., 0.5 mm. copper plus 1 mm. aluminum filtration, and 50 cm. distance. These factors produced an output of 40 r per minute, half-value layer, 0.88 mm. copper and effective wave length of 0.17 Å. A dosage of 200 r measured in air, was given every other day until 3 treatments had been given. This total of 600 r constituted a series. The basal metabolic rate was determined in 1 month and further therapy depended upon the findings. Many of the patients reported by Harris received 2 series of radium therapy and 10 series of x-ray therapy. Radium therapy was applied in dosages of 1000 mg.-hr. to each of 2

lateral areas to constitute a series. The radium pack was at a distance of 4 cm. and the filtration was 2 mm. of platinum or equivalent. One month was allowed to elapse before additional treatment was given.

Harris favors treating the following types of cases: (1) Postoperative recurrences; (2) those with mild to moderate degrees of hyperthyroidism in which the predominating symptoms is nervousness and in which there are no evidences of visceral damage, those associated with little or no loss in weight, and those with slight to moderate thyroid enlargement and in which the goiter is not hard to nodular, (3) those of children with toxic symptoms are treated, except those with nodular goiters, (4) those of patients who are poor operative risks and to whom the irradiation is given as a preoperative procedure, and (5) those in which the patients refuse surgery.

The authors reported their work in 1926 and now report upon an additional series of 154 patients with toxic goiter. Of these, 70.1 per cent showed clinical improvement and reduction in metabolic rate, the remainder were unchanged. The authors gave 200 r at each treatment with the factors 125 kv. peak, 5 ma., 10 minutes, 16-inch distance, and 6 mm. aluminum filtration, effective wave length 0.25 Å. Three portals were used, 1 anterior including the thymus area, and 2 lateral areas. One portal was treated each day for 3 successive days. In cases that proved refractory it was found to be useful to vary the technic by increasing the voltage to 200 kv. with 0.5 mm. copper and 1 mm. aluminum. The effective wave length with these factors is 0.15 Å.

It is important to individualize the treatment of each case, observing the

clinical course and making frequent basal metabolism determinations.

On the basis of their experience the authors do not favor radiation treatment of children. Neither do they favor radiation of goiters which produce mechanical destructive effects on neighboring structures or of goiters with cystic changes. Male patients and elderly patients with increased metabolism do not respond well to radiation.

Hospitalization preceding, during and for a few days after the initial series, is desirable though not imperative. Lugol's solution should be discontinued 2 weeks preceding irradiation, because it confuses the results of irradiation. It is found that 220 r is an adequate dosage to any 1 area in any 1 series. The value of altering the technic arises from the fact that there may be only an isolated portion of the thyroid gland which requires suppression of its activity. This portion may be uninfluenced by radiation with one technic, but influenced with another.

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SURGERY OF THE SYMPATHETIC NERVOUS SYSTEM

By PAUL G. FLOTHOW, M.D.

ESSENTIAL HYPERTENSION

Surgical Treatment—The surgical treatment of essential hypertension continues to be a subject of great interest to both the internist and the surgeon, and conflicting reports continue to emanate regarding the efficacy of the treatment. A great deal of experimental work has

been done which might indicate that the operative treatment is not based on firm physiologic bases. However, this experimental work has been done on animals, making reliable conclusions impossible because undoubtedly the psychogenic and emotional factors which play so great a part in human essential hypertension can-

not be duplicated in them, and the type of hypertension cannot be duplicated. For these reasons we do not feel that the results of this experimental work should be accepted as applicable to the study of essential hypertension in human beings.

Allen and Adson¹ have answered many of the objections to extensive sympathectomy for essential hypertension.

Leriche² has discussed the subject of essential hypertension, and feels that the most effective method of treatment is *splanchnic resection* on one side, and *hemisection of the adrenal* on the other. This is not in accord with the opinion of the majority who do this type of work.

While it is undoubtedly true that a large percentage of patients who have been subjected to operative procedures do not exhibit a permanent decrease in blood pressure, it is also true that approximately an equal percentage do have excellent results that are apparently permanent.

Too frequently opinions as to the value of this treatment are based upon the observation of those cases which might be classed as failures by reason of the fact that their blood pressures are not materially lowered. Those of us doing this work, however, cannot be convinced that it is not of value, since we have all had experience with cases in which the results have been excellent.

In all of the REVIEWER's cases it has been almost invariably true that the patients have been clinically and symptomatically markedly improved regardless of the effect on blood pressure readings. He has come to the conclusion that the results of the operation cannot be measured by manometric blood pressure determinations, and that many cases, which for purposes of statistics are classified as fair or poor results, should not be so

classified. He feels that the operation produces results upon factors in the underlying causes and the associated effects of hypertension which we have no means of measuring.

One case may be cited as an example of such effects. A man, age 32, who had been discharged from the navy because of hypertension and the fact that he was suffering from severe headaches, shortness of breath, fatigability, etc., desired operation. All of the preoperative diagnostic tests indicated that his should be an unfavorable result, and he was advised against the operation. He insisted upon it, however, and offered himself as an experimental case. Before he left the hospital his blood pressure was 260/160, which was exactly the same as his preoperative levels. Four months later this man came in stating that he felt as well as he ever had in his life, and asked for a letter to the navy recommending reinstatement. He said that he could do as good a day's work as he had ever done, and that he had no complaints or symptoms. His blood pressure was still 260/160. His eyegrounds, which had showed hemorrhages before, were entirely clear, and in every way except for his blood pressure readings he was perfectly well.

One thing seems quite certain; namely, that even though postoperative pressure may approximate preoperative pressures, the extreme pinnacles of pressure that had occurred before have been eradicated, as well as many or all of the subjective symptoms of the disease.

Since there is no other type of treatment which offers results in any way comparable to that of the surgical treatment, the work should certainly be continued and, perhaps as time goes on, definite criteria may be evolved for more accurate selection of cases so that failures will become less and less frequent.

MULTIPLE SCLEROSIS

Surgical Treatment—In the past year numerous articles have appeared on multiple sclerosis, particularly in the English literature. Koch and de Savitsch³ report 15 cases upon which they had operated, and 10 of them had been done from 6 to 14 months before the report. They state that practically every patient responded favorably to *cervicodorsal sympathectomy*, and that in most of them there was a marked degree of improvement. All were in an advanced stage of the disease. Two deaths were reported: 1 due to embolism, and 1 as a result of hemorrhage following a slipping of the ligature from the thyrocervical trunk.

The REVIEWER⁴ has reported, in a somewhat similar vein, 20 cases of multiple sclerosis. These cases were operated several years ago, and sufficient time has now elapsed to permit rather definite conclusions. It is his opinion that in the majority of cases the favorable results seen soon after operation are not permanent. The percentage that have a permanent improvement as a result of operation will probably not exceed 40 per cent. In a few cases the results have been so startling that the failures are bearable. One thing he feels is true is that in a great majority of cases the rate of progression has been very materially reduced. Although there is no marked degree of improvement, it seems quite definite that the condition remains at a standstill rather than following the typically progressive course. Anyone doing this operation must be willing to accept what the patients feel is a failure in a large percentage of cases

ANGINA PECTORIS

Surgical Treatment—Berard⁵ reviews the various surgical methods of

treating angina pectoris, and comes to the conclusion that *resection of the stellate ganglion*, or resection of the stellate ganglion plus the upper thoracic ganglia, is the most effective operative procedure. He feels that *paravertebral alcohol injection* is effective in 90 to 100 per cent of cases, but that it is more dangerous than simple novocain of the stellate ganglion, which is usually effective for weeks or months, and can be repeated as often as necessary. He sets forth the experimental bases which have proved that the work on the sympathetic nerves in angina pectoris is physiologically sound both as to the question of pain relief and as to improvement of coronary blood supply

Flothow⁶ also reviews the various methods of treating angina pectoris, and concludes that *cervicodorsal sympathectomy* is the method of choice in younger patients without demonstrable coronary disease, and that paravertebral alcohol injection should be chosen in elderly individuals with coronary involvement

It seems that the question of treatment of angina pectoris has been greatly neglected as it is one field in which surgery or injection of the sympathetic nerves has proved markedly successful.

EXOPHTHALMIC GOITER

Surgical Treatment—A surgical clinic by Professor Jaboulay⁷ is of the greatest interest. He feels that in some way the cervical sympathetic nerves influence the secretory activity of the thyroid gland. Section of the cervical sympathetics relieves the exophthalmos. He feels that *cervical sympathectomy* is a rational procedure in the treatment of exophthalmic goiter, and makes the flat statement, "The method of choice in the treatment of Basedow's disease is,

and must be, section of the cervical sympathetics." He states: "We do not know exactly what Basedow's disease is, but 1 fact seems to be certain, namely, that the cervical sympathetic is the natural and habitual intermediary between the causal element (whether the cause be in the nervous centers, in a gland, or in the nerve itself) and the peripheral organs, the eye, the heart and the thyroid body, whose physical modifications or functions permit the clinician who has observed them to substantiate the disease in question. This intermediary being eliminated, the cause is incapable of producing the peripheral symptoms unless a new intermediary be produced" He reports that sympathectomy has given satisfactory and permanent therapeutic results in all of his cases.

He states. "It must be concluded that Basedow's disease represents the picture of an intense excitation of the cervical sympathetic nerves" He reports a number of cases, particularly of recurrent exophthalmic goiter after thyroidectomy, cured by cervical sympathectomy, and strongly emphasized the fact that they have been *cured* He states further that all cases of exophthalmic goiter that he has operated upon by cervical sympathectomy have been markedly improved, but that the indication par excellence is the case of exophthalmic goiter sans goiter, and that all of these cases are cured He is very enthusiastic about the results in all cases, but most in the cases of exophthalmic goiter without enlargement of the thyroid gland He emphasizes the fact, furthermore, that it is absolutely essential that the condition be not a neurosis since in neurotics the operation is of no value He is convinced after an experience of operating on 11 cases that sympathectomy is the procedure of choice in exophthalmic goiter, especially where there is no enlargement of the

thyroid, and states that if a goiter does appear afterward, it can be removed very safely, as all of the dangerous effects upon the heart and nervous system have been entirely eliminated by the cervical sympathectomy.

It is well to note that this is an opinion of Jaboulay's based upon work done in the late nineties and early twentieth century. It is given at this time to call the attention of the reader to the fact that an old master was thinking constructively many years ago. What he says is well worth reading and well worth considering, since there is no question that his statement that the symptoms of exophthalmic goiter are those which represent an intense excitation of the cervical sympathetics is entirely true. It is not amiss at this time to reintroduce this subject perhaps as a basis for further work, since it is quite generally admitted that the operation for removal of a portion or of most of the thyroid gland is but an intermediary step between the actual cause of the disease and its effects rather than an attack upon the primary etiologic factors

ABDOMINAL PAIN

Surgical Treatment—Diez⁸ reports a new operation for the relief of abdominal pain He resects both the splanchnic and the upper 3 lumbar nerves bilaterally, and states that this operation suppresses all pain except that of the pelvic viscera According to Diez, this operation is indicated in any incurable abdominal disease causing intractable pain, but it is especially indicated in cases of incurable cancer. Leriche and Fontaine also report cases of *intractable pain* relieved by *section of the splanchnic nerves*. The REVIEWER has had a personal experience in this type of case. A

number of years ago he had a patient suffering from an inoperable carcinoma of the pancreas. This man had a palpable abdominal mass which had been explored and the condition found inoperable. He was suffering intense abdominal pain, requiring the continued use of large doses of narcotics. On the basis of the physiology of abdominal pain, which will be discussed later, the REVIEWER injected the celiac and splanchnic area bilaterally with *novocain*. Following this injection there was complete relief of pain and the exquisite tenderness to palpation present before injection had disappeared. By reason of this result, alcohol was injected, and this man lived several years completely relieved of pain and entirely without the use of narcotics.

If our anatomic and physiologic concepts are true, any pain originating within a viscus or an abdominal organ must reach conscious centers by way of the splanchnic and sympathetic nerves. All sensation from the abdominal viscera must go this way unless the parietal peritoneum is involved. Therefore, resection of the splanchnic and upper lumbar sympathetic nerves should of necessity relieve any pain of this type. The pelvic organs, of course, due to the different innervation are not included in this observation.

PULMONARY TUBERCULOSIS

Surgical Treatment—Gaudier⁹ describes the results of *resection of the second and third thoracic sympathetic ganglia* in the treatment of pulmonary tuberculosis. He states that the resection of these ganglia is followed by anatomic modifications in the lung which appear to influence the pulmonary parenchyma favorably. He asserts that experience in this type of surgery may extend the indications to include bron-

chiectasis and pulmonary abscess, and feels that the operation aids in producing the desired effect of pulmonary immobilization and cicatrization.

APOPLEXY

Mackey and Scott¹⁰ *infiltrated the stellate ganglion* in 19 cases of apoplexy with a clinical improvement in each case. In 1 case the improvement was very dramatic, and according to the report could not be doubted. In another case improvement was slight, but, they felt, very definite. They feel that the results do not justify the adoption of the method as a routine procedure, but that further study is necessary before the treatment either can be accepted or rejected. If the treatment is used in severe cases and in elderly individuals, it will only bring the method into disrepute, and they state definitely that it should be used only in milder cases in young individuals. The ideal case is that of cerebral embolism in the young patient, and it should always be done within 24 hours, otherwise the benefits are negligible.

(REVIEWER'S NOTE—From their description, it seems quite definite that the cases in which a good result is obtained are those in which cerebral vasospasm plays a major, or at least an important, part in the production of symptoms. It is difficult to conceive of a real hemorrhage of the lenticulostriate artery being benefited by any procedure directed toward the sympathetic ganglia. There is not much question that so-called stroke or apoplexy in young individuals, or even that classified as a mild stroke in older individuals, is in some cases due to cerebral vasospasm, and in this type of case the rationale of this procedure is based upon definite anatomic and physiologic bases.)

CAROTID SINUS SYNDROME

This subject is included here since the carotid sinus undoubtedly is largely a sympathetic nerve mechanism. Robinson¹¹ has studied 1000 cases of epileptics to determine what relation the epileptic seizure has to the carotid sinus. In only 9 of these cases did he find the carotid sinus syndrome present. The effect of the carotid sinus mechanism can, therefore, be considered as quite negligible in the production of the convulsive seizure. The authors found *benzedrine sulfate* of distinct value in depressing the carotid sinus reflex phenomena.

The so-called carotid sinus syndrome, while undoubtedly a rather rare condition, is a most interesting one. In these cases, most of which are undiagnosed for long periods of time, the most striking feature is the fact that these people suddenly lose consciousness for no apparent reason. These attacks of syncope, which occur when due to a hyperactive carotid sinus reflex, are easily reproduced by pressure upon the bifurcation of the carotid artery in the neck. Interesting cases have recently been reported by Soma Weiss¹² and Patricelli.¹³ The REVIEWER recently operated on a patient in whom the diagnosis had been overlooked for 10 years. The patient was referred by an internist who had reproduced the typical attacks of syncope by pressure on the left carotid sinus. The syncope could not be produced by pressure on the right carotid sinus. Op-

eration with stripping of the common carotid and the internal and external carotids has to date been remarkably effective. The patient still feels that the unoperated side is abnormal. However, pressure on either carotid sinus does not now produce the syncope.

POTT'S DISEASE WITH PARAPLEGIA

Since Diez's report in 1929, Jiana and his associates have performed 2 *lumbar sympathectomies* on cases of advanced Pott's disease with paraplegia with excellent results. They feel that the results are due to the increased blood supply which ensues following sympathectomy.

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THYROID SURGERY

By MOSES BEHREND, M.D, and ALBERT BEHREND, M D

Several authors have discussed some of the more uncommon pathologic lesions affecting the thyroid gland. Kirshbaum and Rosenblum¹ report a case of sup-

purative intrathoracic goiter. Inflammations affecting the thyroid gland usually take the form of simple thyroiditis which may follow in the wake of an upper res-

piratory infection. They usually resolve. Cases of suppurative thyroiditis are rare and may require surgical intervention. A case which the authors report was a sequel of lobar pneumonia. The patient died suddenly 5 weeks after admission to the hospital, despite surgical drainage.

Riedel's struma and struma lymphomatosa are discussed in an interesting article by McClintock and Wright.² The authors have made an exhaustive study of both conditions and believe that they are different and distinct entities.

<i>Riedel's</i>	<i>Hashimoto's</i>
Sex: No difference	95 per cent women
Age: Average age 40	Average age 49
Duration: Average symptoms 7 months	Average symptoms 16 months
Involvement:	
Frequently unilateral	All reported bilateral
Hypothyroidism: 26 per cent postoperative	Over 75 per cent postoperative
Origin Inflammatory	Degenerative?
P E.. Tender and very hard	"Resilient firmness"
Histology Marked diffuse sclerosis with varying number of persisting acini Focal accumulations of lymphocytes occur	Extreme lymphoid infiltration of glands with some evidence of fibrosis. Atrophy of acini

Twelve cases are presented in this review, 4 being cases of Riedel's struma, 4 of Hashimoto's disease and 4 tumors of thyroid gland with giant cell formation

Wilensky and Kaufman³ report 2 cases of an unusual tumor in the thyroid gland, composed of cells first described by Hurthle in 1894 as occurring in normal thyroid gland tissue. Since that time several similar tumors have been noted consisting of the "large oxyphilic parafollicular thyroid cells" which he described. There is some evidence to indicate that these tumors have their origin in parathyroid structures. There are no diagnostic clinical characteristics asso-

ciated with such tumors. In 12 recorded cases, 4 benign and 6 malignant Hurthle cell tumors are described. It is suggested by the authors that the term Hurthle cell tumor be discarded and replaced by the terms adenoma with Hurthle cell change and adenocarcinoma with Hurthle cell change.

Krafka⁴ reports a case of intratracheal thyroid tissue found accidentally in the routine examination of a 7-month-old fetus. The condition is rare and in children that live is usually discovered as a result of the obstructive symptoms it causes. Krafka's case seems to indicate that an early abnormal fixation of the thyroid about which the cartilages form rather than a true invasion of thyroid tissue from without the trachea represents the origin of these growths.

Diagnosis—McMillan and Wendkos⁵ have called attention to the importance of correct and early diagnosis of hyperthyroid states. In a small percentage of cases the diagnosis is obscured by other factors. Thus hyperthyroidism may be masked and the symptoms of hyperthyroidism are never strikingly shown. In such cases, loss of weight is a cardinal symptom and fluctuation in weight of as much as 10 pounds should suggest the possibility of hyperthyroidism. Lahey has pointed out that nervousness and excitability are not requisite in the diagnosis of hyperthyroidism and few patients show a high metabolic rate with an apathetic personality. The authors report a case in which a weight loss of 100 pounds occurred in 3 years. The patient was not stimulated, showed no tremor and no eye signs and yet responded as a typical hyperthyroid case to the administration of Lugol's solution. The changes incident to old age may also mask hyperthyroidism. Marked weight loss, tremor and heart failure are not unexpected findings in the aged and in many cases

the thyroid gland is little if any enlarged. One must be alert to the possibility of such cases and remember that, while they are easily overlooked, most of them show a beneficial response to the administration of iodine. Hyperthyroidism must always be suspected even in elderly subjects who show unusual weight loss, acceleration of the heart rate or unexplained auricular fibrillation.

Jackson⁶ calls attention to the fact that cases are operated upon not infrequently under the mistaken diagnosis of hyperthyroidism. Such conditions as simple goiter, nervous and physical exhaustion and menopausal states must be carefully evaluated before patients are submitted to operation. The metabolic rate should not be taken too literally and the test in doubtful cases should be repeated several times. Finally the failure to respond to iodine should rule out the presence of exophthalmic goiter if the patient is not iodine fast.

Basal Metabolism Determinations

—Boothby, Berkson and Plummer⁷ present a valuable statistical study on the value of B. M. R. determinations. They emphasize the importance of establishing a normal standard value of B. M. R. for male and female patients. They emphasize, too, the importance of the realization that the relative probability of any specific disease indicated by a given finding of metabolism will be in proportion to the actual numbers with this metabolism in disease. Thus during 1917 to 1926, 3385 females with exophthalmic goiter, 3693 with adenomatous goiter and only 136 with myxedema were tested. Clinical observation must play a large rôle in the evaluation of B. M. R. studies, particularly in those whose readings are in the minus group. Most of the patients examined at the Mayo Clinic with a B. M. R. between minus 15 and 20 per cent do not have mild myxedema, but

rather are normal individuals so far as their metabolic rate is concerned. It must be recognized that "basal metabolism," as an actual observation under any defined standard condition, is variable, like any biologic observation and in consequence no one lowest metabolism has a prerogative to be considered the basal metabolism over any other measurement under the defined conditions.

Impedance Angle—Probably the newest diagnostic aid that has been suggested in the study of hyperthyroidism is the so-called impedance angle or electrochemical test of the measure of thyroid function as advocated by Brazier. This has been investigated by Barnett.⁸ The test depends on the differences of conductivity of electric current through the tissues of hypothyroid, normal and hyperthyroid subjects. As a result of his investigations, Barnett concludes as follows: "The thyroid surgeon is being daily confronted with borderline and doubtful cases wherein the B. M. R. is out of line with clinical impressions or where the clinical picture is very vague or complex. What he wants is a method which will lead him out of the difficulty. The Brazier method, in its present state, is unable to do this and in certain cases may even give indications which lead to additional doubt. The truth of the matter is that, at the present time, electrical methods for diagnosing thyroid disease can be said to be still in the developmental stage. When all is said and done, the B. M. R. when properly determined, is the only method which has been sufficiently tested to warrant any real confidence." Future developments along the lines of electrical diagnosis of thyroid disorders will be watched with interest and the method may provide an additional diagnostic aid.

Iodine Studies—According to Taylor,⁹ there is in cases of hyperthyroidism

often an increased amount of iodine in the gland. The normal thyroid gland is able to store its iodine bearing principle, namely thyroxin, but the hyperactive gland is unable to store iodine and pours this substance in the blood stream. The administration of iodine to hyperthyroid patients, however, temporarily at least enables the gland to store thyroxin and its iodine content rises, its histologic picture approaches the normal pattern again, and the blood iodine level falls.

Lerman¹⁰ comments that in a series of 1187 patients, 34 per cent failed to respond to iodine. The operative mortality in this group was 24 per cent. The mortality in cases of hyperthyroidism that respond favorably to iodine was 11 per cent. The most common cause of death in patients who respond to iodine favorably is thyrotoxic crisis. In the nonresponsive group, death commonly occurred as a result of cardiac failure. Lerman finds that males respond less frequently to iodine than females and the mortality among the males is almost twice as great. More commonly, failure to respond to iodine was found in the nodular type of goiter and in patients suffering from heart disease.

Curtis and Puppel¹¹ observe that following subtotal and total thyroidectomy there is an increased loss of iodine in the urine of patients who have been uniodized prior to operation. This loss is not one that is peculiar to the operation of thyroidectomy but is also seen after such procedures as thoracoplasty, mastectomy and spinal fusion. Davison and Aries,¹² on the other hand, have observed that in their experience there is no benefit to be derived from the postoperative administration of iodine in the form of Lugol's solution after bilateral subtotal thyroidectomy. In their experience a group of cases in which iodine was not given had a milder postopera-

tive course than those in which iodine was given. In their opinion the most important phase of the postoperative treatment is proper dilution of thyroxin as obtained by internal and parenteral administration of fluids.

Comment—The exact mechanism of the action of iodine and the reasons for favorable response following its use in cases of hyperthyroidism are as yet unknown. It seems reasonable to believe that in view of the large amounts of iodine administered preoperatively and of the relatively small amounts which the body can utilize that in most cases an excess of iodine is present in most patients properly prepared for subtotal thyroidectomy. However, we have never seen any ill effect from the administration of iodine postoperatively and continue to use it.

Perkin and Lahey¹³ have observed that a correlation is present between the iodine level in the blood and the duration of symptoms. When the syndrome of hyperthyroidism has been present, however, a year or more, the iodine content of the blood tends to become normal, in association with a depletion of the iodine reserves of the body. When the iodine content of the blood is elevated, a favorable response to subtotal thyroidectomy usually occurs. When the iodine level of the blood is elevated, symptoms were found to have been present from between 1 to 9 months. When the clinical syndrome of hyperthyroidism has been present for 1 year or longer, the iodine tends to fall within the normal range. In none of 305 cases studied had iodine therapy ever been given prior to study.

Preoperative Treatment—Frazier and Ravdin¹⁴ advise that severely thyrotoxic patients have been benefited by the administration of *vitamin B* preoperatively. The nutritional state of the patient is improved because of increased appetite

and weight gain. The time required for preparation of such patients for operation is shortened. Vitamin treated cases show a greater fall in heart rate during preparation, suggesting that vitamin B deficiency may in part be responsible for the tachycardia.

Comment—While it is well known that in most cases of hyperthyroidism the appetite is voracious or at least increased, there is a small group in which anorexia is present. Such cases present the worst possible risk for operation. Studies have shown that in many instances the anorexia is directly dependent upon a depletion of the vitamin B reserves of the body. With the administration of vitamin B the appetite improves, the patient becomes more stable and the risk of operation is decidedly lessened.

Heart in Hyperthyroidism—According to Hertzler,¹⁵ adult patients with toxic goiter who show evidence of "goiter heart," arrhythmia, dilatation, or dropsy, should be treated by **total thyroidectomy**. The author states that postoperative myxedema is no more common than after subtotal operations and when it occurs is readily treated by the administration of **thyroid extract** daily. Total thyroidectomy does insure against the reoccurrence of goiter heart while subtotal thyroidectomy does not.

Careful preoperative treatment of the patient with hyperthyroidism and cardiovascular complications is of fundamental importance. According to Ernstone,¹⁶ treatment should consist of rest in bed, administration of iodine, 5 to 15 minims, 3 times daily, sedatives and high caloric diet. Large amounts of fluid should be given except in the presence of myocardial failure. Digitalis is administered only to patients with auricular fibrillation or congestive failure. Preparation for operation should take from 10 to 14

days. After operation the oxygen tent is a valuable adjunct and 10 per cent glucose intravenously is given up to 3000 cc daily. Digitalis is continued. The development of auricular fibrillation after operation is of little importance and rarely lasts more than 48 hours. When auricular fibrillation is present preoperatively no effort is made to reestablish normal rhythm. In one-third of the patients the rhythm becomes regular spontaneously after operation. In one-half of the remaining patients normal rhythm can be restored by the use of quinidine sulfate.

Operative Treatment—All authors are in agreement with Anderson,¹⁷ who states that all adenomatous goiters should be operated on as early as diagnosis is made. He states that all such patients should have **Lugol's solution** for 10 to 15 days before surgery whether they are hyperthyroid or not. He warns, however, that no patient with adenomatous goiter should receive Lugol's solution unless surgery is contemplated.

Comment—It has been emphasized by C. W. Mayo and others that approximately 90 per cent of carcinomas of the thyroid gland occur in adenomatous thyroids. In a large group of adenomatous goiters approximately 3 per cent will be found carcinomatous.

Preoperative and Postoperative Régime—Thompson,¹⁸ *et al.*, stress the importance of a proper pre- and postoperative régime as a means of lowering mortality of thyroid gland operations. In a series of cases operated upon at the Cook County Hospital it was found that the mortality rate for operation on toxic goiter dropped from 10.8 per cent to 1.6 per cent and for exophthalmic goiter from 13.1 per cent to 1.5 per cent, simply by paying greater attention to the pre- and postoperative care and by restricting the performance of the actual

surgical procedure to men specially trained and qualified in thyroid surgery.

In a group of 161 patients whose hyperthyroidism was severe enough to warrant such operations, McGraw¹⁹ employed a short interval of 7 to 10 days between stages. He believes this procedure has been useful in a group of patients whose educational, economic and financial status did not allow them to co-operate well when operations were spaced at 4 to 6 weeks. The mortality in this group was 7.5 per cent

Comment—There is no doubt that many patients have been saved by stage operations and preliminary ligation of the superior thyroid arteries. However, it appears highly probable that patients who are able to withstand 2 major thyroid operations within a period of 7 to 10 days would have survived a bilateral subtotal thyroidectomy. The mortality rate quoted by McGraw leaves little to recommend the method

Injury to Recurrent Laryngeal Nerves—Lahey and Hoover²⁰ have reviewed the incidence of injury to the recurrent laryngeal nerves and discuss the more common causes for such injury. They advocate exposure of the recurrent nerves in every thyroidectomy as the only sure means of avoiding injury to the nerves. With routine dissection such as the authors advocate, the incidence of nerve injury during thyroid operations has been lowered from 1.6 per cent to 0.3 per cent at the Lahey Clinic. Lahey has also reoperated on patients whose nerves have been cut elsewhere, and successfully reunited the cut ends. He states that it is best to reoperate such cases within 3 months of the original injury

Anesthesia—Brenizer²¹ has recently reviewed a series of 4000 goiters, 3416 of which have been done under local anesthesia. He now advocates cervical

and brachial plexus block as the ideal method for producing anesthesia in operations upon the thyroid gland. Simple infiltration with a local anesthetic over the thyroid gland as formerly practiced was not sufficient to entirely relieve pain and relax muscles. It has frequently been possible to perform thyroidectomy under the nerve block procedures mentioned above without further infiltration of the thyroid gland.

Comment—No set rule can be made as to the ideal anesthesia for thyroid operations. In some hands local anesthesia and cervical block work very well. In others the use of avertin or inhalation anesthetics such as cyclopropane and nitrous oxide is preferred particularly by those surgeons who still regard anoc. association as an important adjunct to successful thyroid surgery. It is our impression that cases in which cervical plexus block has been done drain less freely postoperatively than those cases in which infiltration is carried out directly over the gland.

Postoperative Problems—Dinsmore²² has reviewed the interesting mental manifestations associated with thyroid disease. He warns that when hyperthyroidism and a psychosis are present in the same patient they are independent of each other and the prognosis for the cure of the psychosis is poor, although following thyroidectomy the general condition of the patient will usually improve. He states that psychosis rarely develops after operation or at least not any oftener than after the other operations, and when they develop, in his experience, are not serious. Usually symptoms will be found to have been present before operation. The toxic delirium of acute crises is now less frequently observed than before the days of iodine therapy. If delirium lasts more than 48 hours the prognosis is bad despite the administration of iodine,

glucose, saline or blood transfusions. If the patient is unable to take iodine by mouth or in a proctoclysis because of vomiting or diarrhea he advises that it be given by vein or that it be painted on the skin, through which absorption takes place. A third group of cases are those in which delirium and confusion occur after thyroidectomy associated with liver failure. In these cases the icterus index rises on the second or third day postoperatively. The condition appears more frequently in patients past middle life. Associated with evidence of liver failure may be a diminished renal function. Occasionally cases of hypothyroidism postoperatively are observed showing drowsiness, peculiar glistening of the skin, nervousness, numbness and tingling of the extremities. Dinsmore advises 6 to 10 grains (0.4 to 0.6 Gm.) of *thyroid extract* be given to such patients. In a large series of postoperative hyperthyroid cases approximately 2 to 3 per cent will develop recurrence of symptoms. Enlargement of the gland is not always palpable because it is usually at the upper pole and may frequently be posterior or intrathoracic. Some of these cases are controlled by the administration of *iodine* over long periods.

Clute and Albright²³ have contributed an interesting article on the management of minor complaints after thyroidectomy. They note that pain associated with swallowing usually is due to injury of the prethyroid muscles and is best treated by sitting the patient up in bed on his return from the operating room and allowing the head to bend forward until the chin touches the sternum while swallowing. Formation of intratracheal mucus can best be relieved by inhalations of steam or tincture of benzoin vaporized in hot water. Small doses of *morphine* are helpful as are small doses of *atropine*. Some patients complain of a sense

of a lump in the neck which may be due to edema of the prethyroid tissue or to a secondary collection. Such collections must be prevented by careful hemostasis. For this purpose the authors use 000 catgut rather than silk. When hematomas do occur they must be opened promptly. Pain across the back of the neck and down the shoulders may be due to hyperextension of the cervical spine and responds well to the use of codein and aspirin. Voice changes may follow operation as a result of congestion of the mucous membrane of the larynx and trachea, postoperative mobility of the larynx, or temporary injury to the superior and inferior laryngeal nerves. When keloids develop in a scar following thyroidectomy they are difficult to remove. The authors have tried excision, radium and x-ray treatment without perfect results. They now use skin clips, removing half in 24 hours and the remainder in 48 hours.

Comment—Silk ties and sutures were used by us many years ago and abandoned. Recently we took up the use of silk ties again. We have again abandoned them because of the sinuses which occurred following their use. We now use fine catgut. We have tried electrocoagulation of the small vessels and have given this up because it was commonly followed by a collection of a large amount of serum. The use of clips and their method of removal as advocated by Clute and Albright receives our enthusiastic support. Clips leave almost invisible wounds. For the last 10 years we have drained very few cases after thyroidectomy. In about 50 per cent of these a small amount of serum accumulates which is readily released by a probe.

Cancer

Treatment—Graham²⁴ has noted a tendency of carcinomas of the thyroid

to perforate the thin walled veins of the tumor and extend into the main thyroid veins. Appreciation of this fact is necessary for intelligent treatment of recurrences of carcinoma of the thyroid. He advises general anesthesia, **wide excision of recurrent nodules** without breaking into the mass or leaving remnants in the wound and removal of tributary veins. He warns: "The first operation for the removal of the recurrence offers the best and perhaps the only opportunity for a cure." In his cases radium and roentgen therapy were ineffectual in preventing recurrences

According to Foss²⁵ the incidence of malignant disease of the thyroid gland among goiters of all types, from the reports of 11 authors, is 2.37 per cent. They may be classified as papillary adenocarcinomas, adenocarcinoma in malignant adenomas, diffuse adenocarcinomas, epithelioma and sarcoma. In most instances they are not recognized until after operation, when the tissue have been examined in the laboratory. Broders warns, "Of all adenocarcinomas in any situation, I know of none with a wider range of structure than adenocarcinomas of the thyroid. They may be so undifferentiated that they are with difficulty distinguished from sarcomas, and, on the other hand, they may be so differentiated that they produce structures closely resembling the normal thyroid gland, toxic adenoma, or exophthalmic goiter, with the actual production of hyperthyroidism." Eighty-five to 90 per cent of all carcinomas originate in pre-existing adenomas. Consequently adenomas should be removed as a prophylactic measure. The treatment of choice is **early operation** and **total extirpation** of the carcinoma by **irradiation**.

Other Methods of Treatment—
Roentgen therapy as a means of treating exophthalmic goiter is discussed by

Poulton and Watt.²⁶ They state that the use of deep x-rays has been prejudiced by earlier failures of radiation and the increasing successes of surgical intervention. In young subjects the present treatment consists of 1 course of deep therapy and this should effect a cure. In severe cases the first course is followed by rest in bed for 10 to 12 days. A second course similar to the first is given at the end of this time and this is followed by a 1-month rest in bed. Results of such therapy should be noticeable in 3 months. If the patients improve markedly, further treatment is postponed for 3 months. If improvement is only moderate, a second course of treatment is given. Should the symptoms persist at the end of a year it must be decided whether to use a third course of treatment or to resort to other methods. The authors conclude that modern deep therapy is an efficient method for the treatment of toxic goiter. It is useful in the treatment of recurrences after operation and it should play a special rôle in the young and in the grave type of disease. The treatment is not dangerous to life and good results appear to be more or less permanent. As in many other diseases it should work hand in hand with medicine and surgery.

Jaboulay²⁷ has operated upon several cases of Graves disease by directing attention to interruption of the fibers of the cervical sympathetic nerves. He was first led to do this procedure in a patient who had been operated upon 5 times in 3 years for recurrent hyperthyroidism. **Section of the cervical sympathetic nerves** causes the eyes to return to their orbits and the pupils to contract, diminishes the volume of the thyroid gland and retards the beat of the heart. The operation is particularly recommended in so-called cases of exophthalmic goiter without goiter. Joboulay concludes that

the operation is a good one particularly in elderly patients but it gives good results in all types of hyperthyroidism. The superior cervical ganglion is approached through an incision in the neck behind the sternocleidomastoid muscle and for best results he advises removal of the middle and inferior cervical ganglion in addition.

Diet—The question of the place of diet in the treatment of hyperthyroidism is raised by an interesting case reported by Soskin and Mirsky.²⁸ They treated a patient who had refused surgical treatment of severe hyperthyroidism by means of a *high fat diet*. The patient was put to bed in the hospital and a control diet was given for 2 weeks consisting of protein, 80 Gm ; fat, 80 Gm ; and carbohydrates, 400 Gm ; total calories, 2640. Under this diet no improvement occurred. Then a diet consisting of protein, 90 Gm ; fat, 230 Gm , and carbohydrates, 90 Gm , total calories, 2790 was given. There was a gradual regression of signs and symptoms of hyperthyroidism. In 5 months the patient showed no symptoms, signs, or laboratory evidence of hyperthyroidism. She has remained on a high fat diet without a return of symptoms and her weight has been constant at 130 pounds.

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UROLOGY

By ELMER HESS, M.D

Introduction—Advances in the diagnosis and treatment of urinary tract pathology have been made during the past year.

The diagnosis and treatment of *cortical and medullary tumors of the adrenal* have been placed upon a more scientific basis and much improvement is noticed

in the results of our surgical measures for relief of these conditions.

Neurogenic dysfunction of the bladder can be relieved very often by such drugs as mecholyl and prostigmin. More radical surgical attack on the sympathetic nerve supply may be necessary and painful bladder lesions may require bilateral sacral ganglionectomy as well as presacral neurectomy.

There is nothing new in the treatment of bladder tumors but results are better because physicians have been educated to have their cases of urinary bleeding cystoscoped immediately. While progress has been made in the early diagnosis of renal tumors, there has been little advance in the treatment of these neoplasms. Some hope may be derived from a few favorable reports of cases treated by pre- and postoperative x-ray and radium therapy.

While perhaps not as marked, it is with just pride that the urologist points to the increased knowledge of chemotherapy in the treatment of urinary tract infections. Sulfanilamide has been carefully studied, and has been found to be a very valuable drug, not only in gonorrhea but also in streptococcal and colon bacillus infections. Particular emphasis has been placed upon the use of this drug in postoperative infections following transurethral prostatectomy.

Concentrated human blood serum has been tried as a diuretic in the treatment of nephrosis, while nephrectomy, where there is local ischemia, seems to produce remarkable results in certain types of hypertension.

A new diagnostic procedure has been suggested in respiration pyelography. It is hoped that this procedure will be of help in the differential diagnosis of perinephric and subdiaphragmatic abscess and also as an aid in further study of renal mobility.

The literature is still filled with the accounts of transurethral prostatic procedures. The method is used favorably in prostatic abscess and in the treatment of carcinoma of the prostate with obstructive symptoms. In the cases of simple hypertrophy of the gland many urologists recommend it for those up to Grade II. In the larger adenomas and where instrumental difficulties are encountered the perineal or suprapubic approach are advised. The hormonal treatment of prostatic hypertrophy is still very much in the experimental stage and is not likely to prove of very much value.

ADRENAL TUMORS

A great deal of interest in adrenal tumors has been manifested recently. Tumors of the medulla are usually benign and are considered active factors in attacks of hypertension. Tumors of the cortex, as a rule, cause sex changes which are due to the increased function of the hyperplastic glandular tissue. Women seem to be the most frequent sufferers, and the changes are in the secondary sexual characteristics. There may be cessation of menstruation, increased and abnormal hair growth, enlargement of the clitoris and other changes which tend toward the masculinization of the individual. The diagnosis of adrenal tumor is one of the most difficult to make. Two factors may aid in the diagnosis. The finding of estrogenic substances in the urine in a non-pregnant woman is suggestive, while in a fairly large percentage of cases x-ray pictures taken after air has been injected in the tissues around the adrenal will be of help. This is a test not without grave danger.

W. Walters and E. J. Kepler¹ state that the treatment of this lesion is, of course, surgical removal of the tumor;

this has been accomplished in 7 cases at the Mayo Clinic without any mortality. Two of these tumors were very large and weighed 600 Gm. and 800 Gm. respectively, while the others averaged approximately 2 to 4 cm in diameter. Although microscopic examination showed early malignant changes in all the tumors, in 5 cases the tumor was definitely encapsulated and recurrence had not taken place. In the 2 cases in which the tumors were very large, penetration had extended beyond the capsule; the growth was attached to the diaphragm in 1 case and to the inferior vena cava in the other case. In both cases the lesions were malignant, there were signs and symptoms of recurrence and both patients died within 2 years after the operation.

Surgical Therapy—The most important factor in surgical therapy is the anticipation, prevention and control of postoperative adrenal cortical insufficiency. This consists essentially of the preoperative and postoperative administration of *potent extracts of the adrenal cortex* and parenteral and oral administration of adequate amounts of a solution of *sodium chloride* and *sodium citrate* and the administration of a *diet* that is *low in potassium*. These procedures tend to control the impending adrenal cortical insufficiency which has probably been responsible for the high mortality (50 per cent previously reported by Lukens and his associates, by Cahill and his associates and by Scholl). The method outlined is essentially that which at the Clinic has been found to be effective in controlling various degrees of adrenal insufficiency in Addison's disease and has been used in all our cases of suspected adrenal cortical tumors. Its effectiveness is illustrated by operative recoveries in 7 cases; in 2 of the cases the adrenal glands on

the opposite side were found to be atrophic. It must also be remembered that the outstanding characteristic of any hyperfunctioning adenoma is its tendency to produce its hormone irrespective of the needs of the body for this hormone. The remaining nonadenomatous endocrine tissue of the type from which the adenoma took its origin can be expected to hypofunction. This remaining nonadenomatous tissue may be functionally inadequate or be actually atrophic on histologic examination. By tiding the patient over the crisis with the administration of potent adrenal extracts and by concentrating the sodium ions in the body, it has been our experience that eventually the nonadenomatous endocrine tissue will regain its capacity to produce a sufficient amount of hormone to meet the needs of the body as regeneration occurs.

In brief, postoperative adrenal insufficiency should be anticipated and should be prevented by continuous treatment throughout the postoperative period; during the entire postoperative period the patient should be watched carefully for any premonitory signs of acute adrenal failure. Among the more important signs of such failure are anorexia, hiccup, nausea, vomiting, weakness, insomnia, apathy or restlessness, an increasing pulse rate and a falling blood pressure. Pyrexia accelerates the development of adrenal insufficiency and is therefore poorly tolerated. These clinical manifestations may precede any material change in the chemical composition of the blood. The blood pressure should be recorded every 4 hours and the concentration of blood sugar, plasma chlorides and blood urea should be determined daily. If, at any time, the condition of the patient is the least suggestive of adrenal insufficiency, more vigorous treatment should be instituted or treatment should be

resumed if it has been discontinued. It is not generally appreciated that fatal adrenal failure can develop within a few hours. In consequence of this fact it is easy for the physician to be lulled into a false sense of security. A good rule of thumb to remember is that danger lies in undertreatment rather than in over-treatment.

BLADDER

Neurogenic Vesical Dysfunction

Both the sympathetic and parasympathetic nerves are parts of the autonomic nerve supply to the urinary bladder. Both systems are necessary to proper motor function of the detrusor and vesical neck and both carry pain impulses. During the past few years many operations have been done, particularly on the presacral ganglia, for various types of neurogenic bladder disturbances with varying results.

F. L. Pearl and B. Strauss² report 3 cases of retention of urine and one of chronic interstitial cystitis (Hunner ulcer) in which the sympathetic nerves were attacked surgically with satisfactory results. Three cases were selected for presacral neurectomy because of markedly weak detrusor muscles, associated, in 2 cases, with spastic internal sphincters; the fourth because of severe pain and frequency due to a chronic interstitial cystitis.

One patient suffered from retention with overflow incontinence accompanying a vascular lesion of the spinal cord. The second patient suffered from retention of urine without overflow accompanying a right hemiplegia with aphasia. The type of vesical dysfunction in this case was different from the usually reported small capacity bladder with increased detrusor tone and overactive stretch reflex occurring in cerebral le-

sions. Both these cases had spastic bladder outlets. Both were able to void spontaneously following operations, although both still carried small residuals. *Presacral neurectomy* was done in both cases.

The third case was one of primary vesical atony with a large infected residual urine, associated with an extensive leukoplakia of the bladder. The detrusor was markedly hypotonic. Following *presacral neurectomy* and *bilateral sacral ganglionectomy* and trunk resection, the infection cleared, the amount of residual urine decreased, and the leukoplakia almost completely disappeared. Leukoplakia is notoriously resistant to any form of treatment.

The fourth case was one of chronic interstitial cystitis of 10 years' duration. It had resisted all forms of treatment except fulguration, which gave but temporary relief. Following presacral neurectomy and sacral ganglionectomy she showed increased capacity, diminished frequency and relief of pain.

When sympathectomy is done for painful conditions of the bladder or for the production of persistent vasodilatation of bladder arteries, it would appear that bilateral sacral ganglionectomy and trunk resection should be done in addition to presacral neurectomy. The latter procedure alone is sufficient for purely motor neurogenic dysfunction. The operative technic should offer no particular difficulties.

Presacral neurectomy may establish voluntary micturition in cases of neurogenic vesical dysfunction with retention which demonstrate a weak detrusor and a spastic internal sphincter. However, the detrusor may remain hypotonic, and the bladder may not empty completely.

Presacral neurectomy increases the expulsive force of the detrusor and re-

laxes a spastic internal sphincter. This effect may be temporary.

Bilateral sacral ganglionectomy is advisable in addition to presacral neurectomy in painful vesical conditions or when prolonged vasodilatation is desired in severe intractable cystitis.

No undesirable effects have been noted following presacral neurectomy and sacral ganglionectomy.

those of spasticity of the internal sphincter and whatever distress may be alleviated by relief of ischemia of the vesical wall. In addition to these, an allied condition, irritable bladder without demonstrable cause, has been relieved by Braasch and Craig, when this operation was utilized.

2. Some degree of relief in painful conditions of the bladder as the result

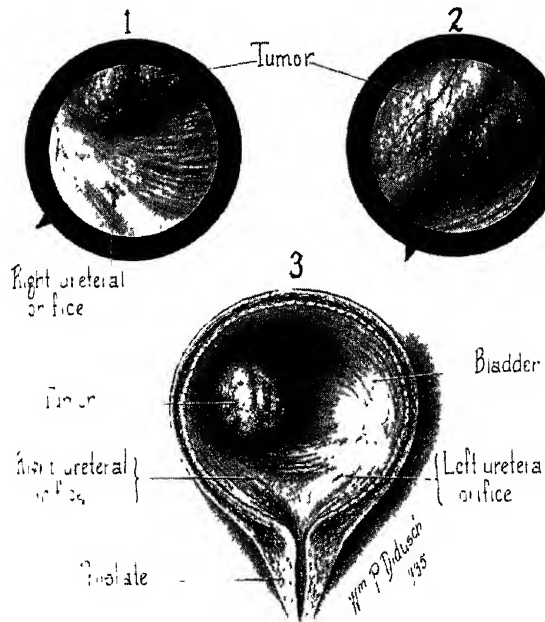


Fig 1—Clamp method Typical tumor of the bladder suited for excision by this method, showing the common position of such a tumor, and its most usual dimensions 1 and 2 Tumor as seen through cystoscope 3 Reconstruction of cystoscopic findings showing position of tumor and approximate size (Thomas J Kirwin The Management of Bladder Tumors Surg, Gynec & Obst June 1938)

Presacral neurectomy has been performed for the following vesical and ureterovesical disorders

1 Learmonth, McConnell, Quinby and Douglass have reported improvement following section of the presacral nerve for interstitial cystitis; however, not all of the patients were completely relieved. As the parasympathetic fibers carry afferent impulses from the mucosa of the bladder, presacral neurectomy can relieve only painful impulses of muscular origin,

of malignancy has been reported by Learmonth and McConnell. This condition is seen in a debilitated patient with a short tenure on life, and it is my impression that the operation is far too drastic. Also, little hope for complete relief from pain can be held, because of the extent of the growth and transmission of painful afferent impulses over a larger distribution than that of the presacral nerve. I have found that the intraspinal injection of alcohol has been far

more satisfactory and it carries a minimum of surgical risk.

3. Ward has reported improvement following presacral neurectomy in cases of hydroureter. Before submitting a patient to this procedure, one should determine definitely that this condition is

organ. The results of cord bladder of nonsyphilitic origin have been more favorable than those obtained in syphilitic patients. Learmonth, Bailey, Calley and Fulcher have reported good results in paralysis of the bladder which followed trauma, congenital defect of the

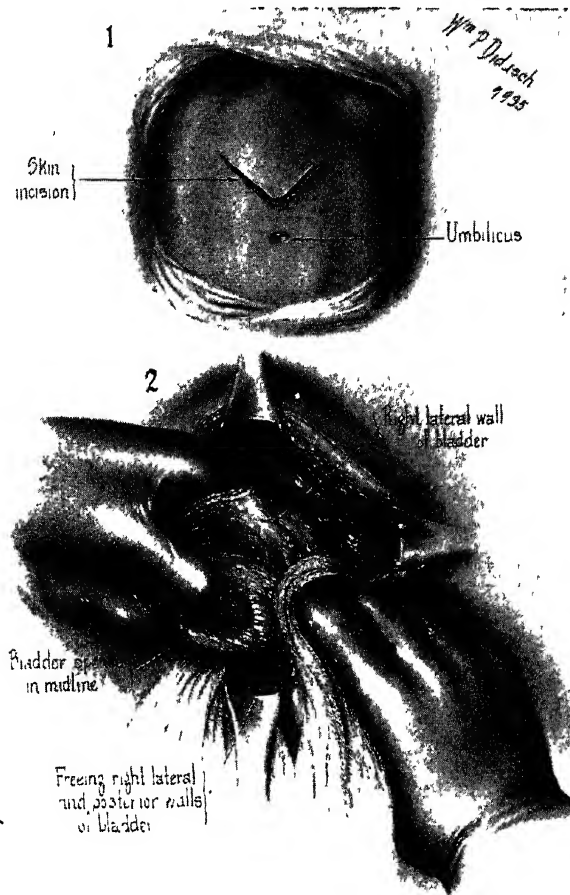


Fig 2—Clamp method Skin incision and the method of freeing the bladder's right lateral wall after it has been opened at the midline (Thomas J Kirwin The Management of Bladder Tumors Surg. Gynec & Obst., June, 1938)

caused by a spastic state of the ureterovesical orifices, so that the operation will be on a sound physiologic basis. I have never resorted to presacral neurectomy in any of these instances.

Paralysis of the bladder may be approached with the thought that the removal of the inhibitory sympathetic fibers may aid in the emptying of this

parasympathetic system, pressure on the cauda equina by tumors, fibrous, fibrocartilaginous or bony structure.

Cord bladder as a complication of syphilis has not responded well in my experience, although Calley and Verbrugghen have met with partial success. It has been my observation that the case of syphilitic cord bladder will receive

ceases at the completion of the menstrual cycle. Its diagnosis should be suspected with such a history. The tumor is diagnosed by cystoscopy. It usually involves

diagnosis is made by cystoscopic examination. Several of the roentgenologists, particularly Pfahler, of Philadelphia, depend for their diagnosis upon the use of

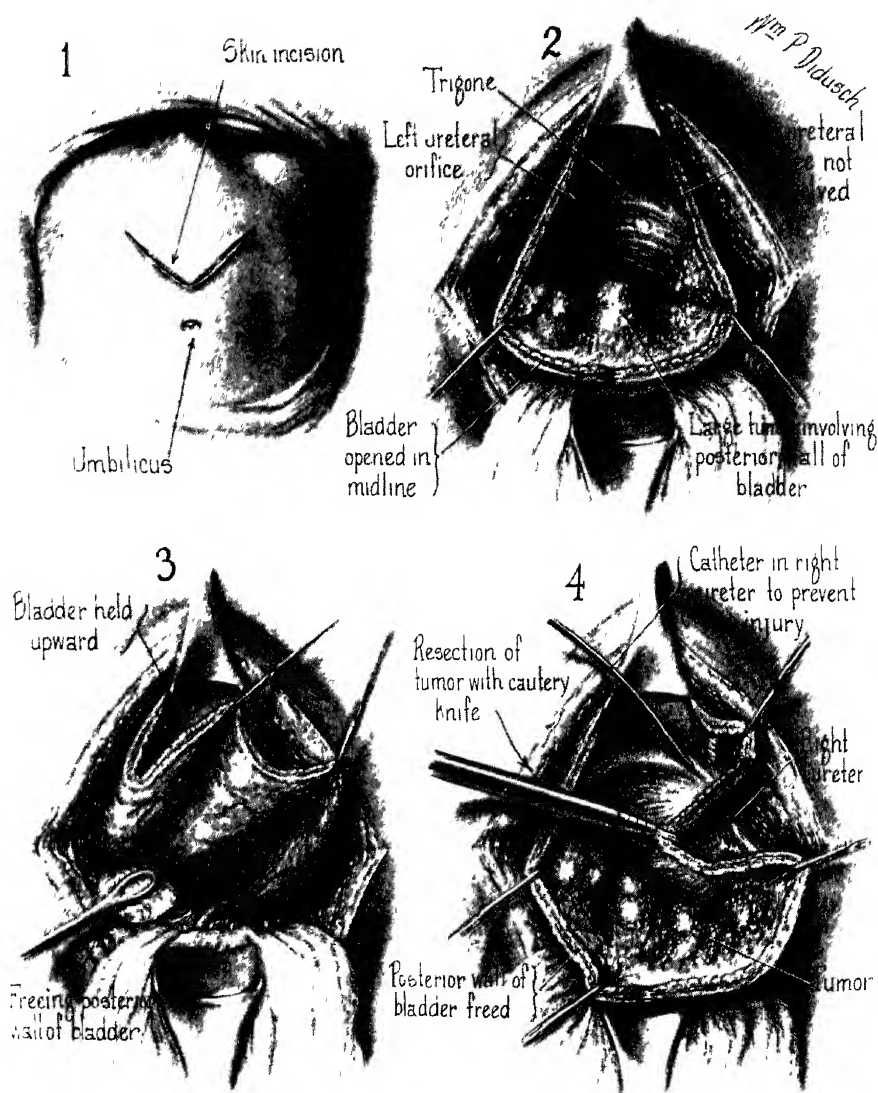


Fig 5—Resection by cauterization. 1 Skin incision. 2 Bladder opened exposing tumor. 3 Freeing posterior wall of bladder. 4 Resection of tumor with electrocautery. (Thomas J Kirwin, The Management of Bladder Tumors, Surg., Gynec. & Obst., June 1938.)

the fundus of the bladder and is well circumscribed.

Hematuria, painless and profuse, with intervening periods of bloodless clear urine is the outstanding feature of all tumors of the urinary bladder. Positive

aerograms of the bladder. This procedure can, of course, never take precedence over the more accurate cystoscopic visualization of the tumor. Before treatment is undertaken it is wise to have an intravenous urogram made in an effort

to ascertain whether or not the bladder growth is secondary to a malignancy of the upper urinary tract. If in doubt, then it is advisable to check the case further

ondary transplants later develop in the upper urinary tract. The editor calls attention to these procedures because in the past year 2 cases of bladder tumor

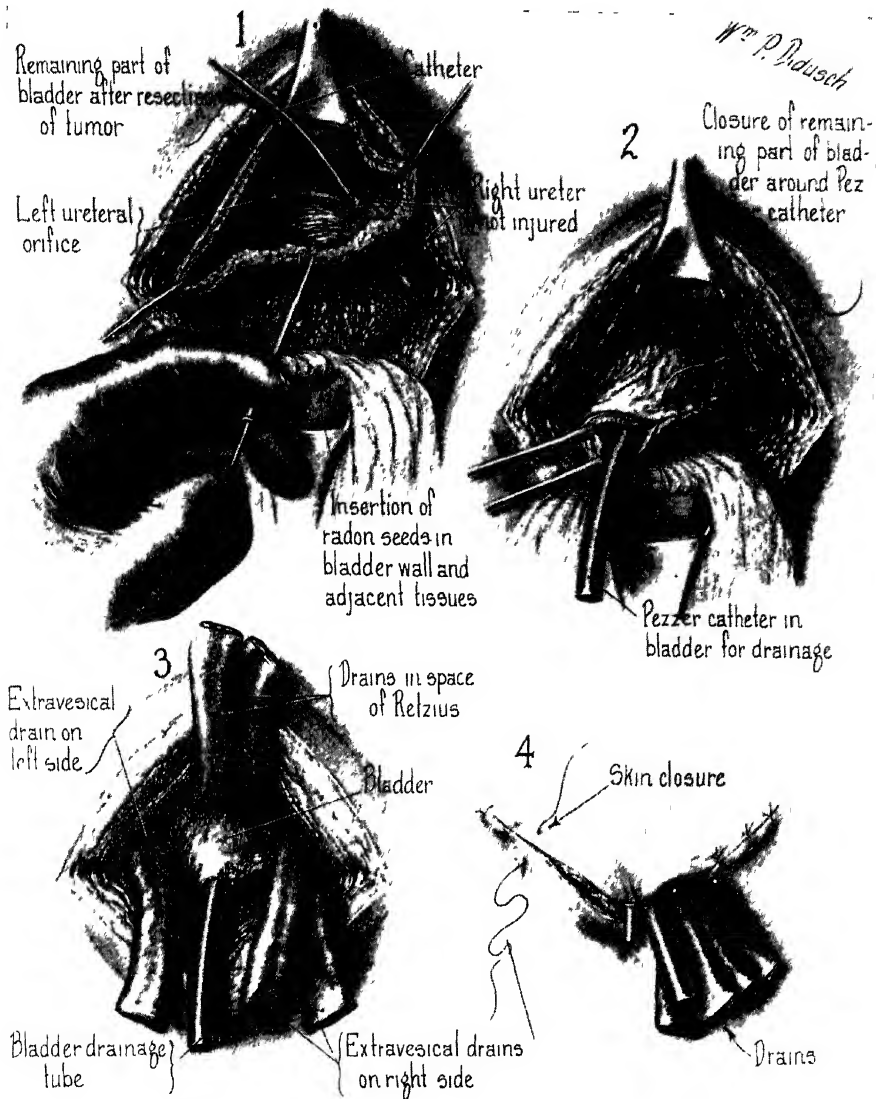


Fig 6—Cautery method 1 Method of “seeding” the cut edges of the remaining portion of the bladder wall before closing it 2 Closure of remaining part of bladder 3 Bladder closed, drains placed 4 Final closing of skin incision (Thomas J Kirwin The Management of Bladder Tumors Surg. Gynec. & Obst., June, 1938)

with a retrograde pyelogram. The latter procedure should not be done unless there is a direct indication for it as it would be possible to carry tumor cells up the ureter and possibly have sec-

were discovered to be transplants from upper urinary tract tumors, neither of which would have been suspected or discovered if it had not been for the use of the routine intravenous urogram in all

cases of bladder involvement. The diagnosis, once made, treatment may be planned.

Treatment—The treatment is variable and depends upon many factors. Inasmuch as bilateral oophorectomy or irradiation of the ovaries removes the

hysterectomy with removal of the adnexa was done, with no attempt being made to excise the growths in the bladder. The operations were followed in each case by complete regression of the bladder growths. In the primary type of tumor, *excision of the bladder lesion* is the

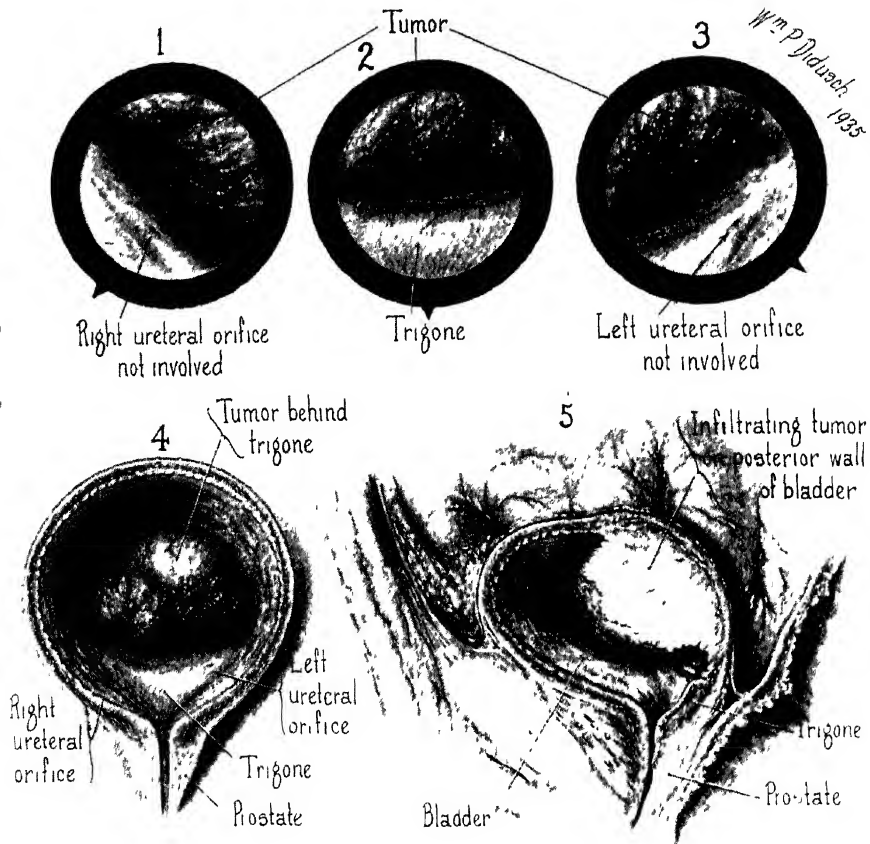


Fig 7—Loop-ball-disc method 1, 2, and 3 Cystoscopic views of a large tumor behind the trigone, infiltrating the posterior wall of the bladder 4 Reconstruction of condition 5 Sagittal section showing position of tumor (Thomas J Kirwin The Management of Bladder Tumors Surg, Gynec & Obst, June, 1938)

hormone stimulation necessary for continued growth of heterotopic endometriomata, *artificial menopause* would seem indicated in patients at or near the menopause or for those in whom there is massive involvement of the bladder, too advanced for successful complete removal. Keene reported 2 cases of secondary involvement of the bladder from the ovaries in which a supravaginal

method of choice in young women desirous of having children. Even in the secondary types of endometriosis of the bladder, excision may be done with a good chance of nonrecurrence. P. S Adams.⁵

If open surgery can be avoided, it is to the patient's best interests. Sections of the average bladder tumor for pathological study can easily be obtained by

the transurethral instruments used for resections. This is clinically not essential as in the average case a skilled cystoscopist can determine fairly accurately the malignancy or otherwise of the tumor from its physical aspects. Generally speaking, a tumor with a small pedicle is benign; with a large one, malignant. Potentially, they are all malignant and, in the editor's opinion, should be so

give good results except in the very occasional case. This is not only the opinion of the editor, but E. W. White⁶ states: "I cannot visualize the justification for any form of radical surgery in the management of bladder new growths, and I feel that every attempt should be made to avoid the inevitable suprapubic fistula, which formerly too frequently occurred." Further quoting White:

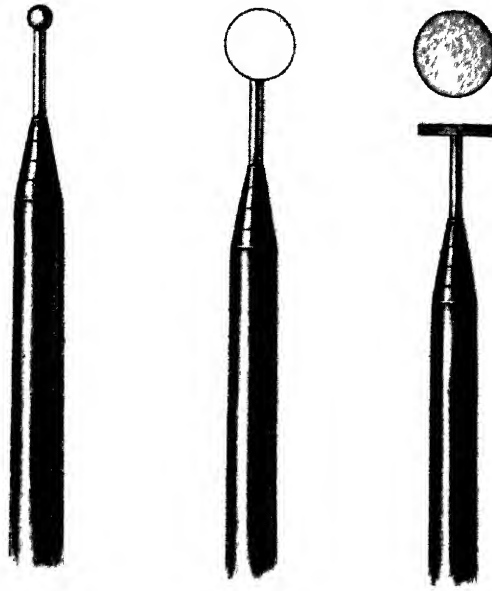


Fig. 8—Details of 3 different electrodes employed in carrying out the technic (Thomas I. Kitwin: The Management of Bladder Tumors Surg., Gynec. & Obst., June, 1938)

treated. If the tumor is so situated that it can be cystoscopically visualized and does not involve the trigone or the internal meatus it does not need to be operated upon. However, if the tumor involves the high lateral walls of the bladder or the fundus, it is as curable by open resection as are tumors of the uterine fundus. There is much in the literature during the past year concerning radical cystectomy with implantation of the ureters into the skin or bowel. In the vast majority of cases when such treatment is really curative the tumor can be eradicated by simpler methods. In the late cases this radical procedure will fail to

"Surgical diathermy is applicable in the therapy of almost all types of bladder and urethral tumors, from simple papillomata to Grade IV cancer."

For simple benign bladder papillomata, visible cystoscopically, *fulguration* or *coagulation* should be applied transurethrally. For large pedunculated growths, fulguration is probably best, the fulgurating point being applied until the growth is destroyed. For sessile growths with large bushy fronds, the coagulating current is advisable. The active electrode is applied first at the circumference and worked downward, as we have found it difficult to attack this type at the base

Fulguration or coagulation may be repeated as often as is necessary or as often as is consistent with intelligent electrotherapy.

For *small localized noninfiltrating papillary carcinoma* which fortunately is slow

and secondly, remove the tumor with a wide area of bladder surface *en masse*. Not infrequently, when in advanced and apparently hopeless cases, the superimposed cancerous growth can be destroyed, leaving a clean granulating sur-

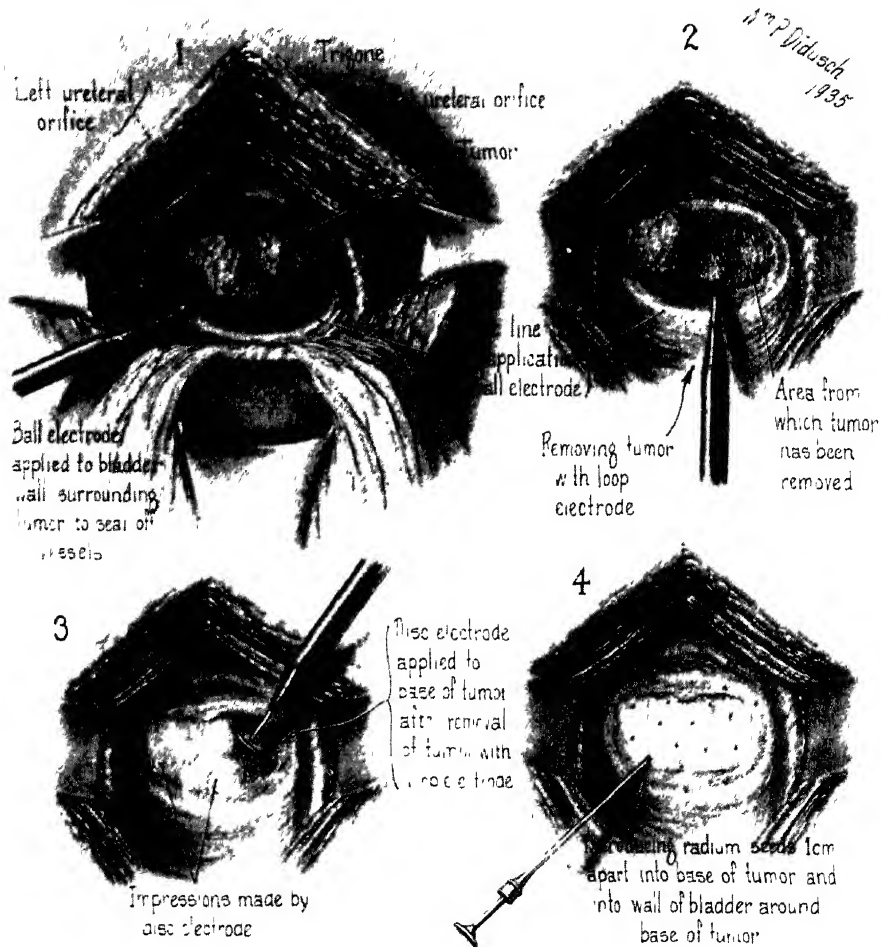


FIG. 9-1. 1. Ball electrode is applied to wall encircling the tumor. 2. Entire tumor mass is being removed with loop electrode. 3. Method of applying the disc electrode to the base of the tumor after the exuberant portion has been excised. 4. Implantation of radon seeds. (Thomas & Kirwin: The Management of Bladder Tumors. Surg., Gynec. & Obst., June, 1938.)

to metastasize, **transurethral coagulation** gives excellent results. In the larger vesical tumors, coagulation should be done through the open bladder. We do not hesitate in certain instances in which tumors are located on the anterior or posterior walls, even if evidently infiltrating, to coagulate through the bladder wall,

face, with diminished bleeding, and great relief to the patient.

In all malignant growths, especially Grades III and IV cancers, the use of **radium emanation seeds** (radon) always should be applied throughout the base of the growth and in the surrounding tissues following coagulation. This

rule applies whether the coagulation is cystoscopically or *via* the open bladder. We have experienced considerable difficulty in the application of radon seeds transurethrally, and in most instances of the larger bladder malignant tumors we prefer and recommend *open surgery* and *diathermy*.

T. J. Kirwin⁷ is in virtual agreement with the above and says: "Effort has been made to demonstrate that adherence to any one technic in dealing with vesical tumors whenever and wherever found is a fundamentally unsound practice. No one method can be adapted to all cases. The principal methods of treating tumors of the bladder are offered which will fulfill the requirements of the conservative practice in the great majority of instances. It is recommended as combining the excellencies of all 3 standard methods, while eliminating the drawbacks to which each is subject when used alone

GONORRHEA

Treatment—Many favorable reports on the treatment of gonorrhea by the use of *sulfanilamide* were reported last year in the literature. To evaluate the treatment of the disease by this drug now seems possible as a result of further studies and observations concerning its specificity. Certainly in the early stages of the acute infection, the drug is very valuable in a large percentage of cases. In some cases its administration seems to have little or no effect. There are a few individuals who seem to have a definite idiosyncrasy to the drug. In these cases the drug may have a beneficial effect upon the disease but its use in proper dosage is distinctly contraindicated. Dizziness seems to be of more importance as a warning signal than is the customary blueness of the lips and

tongue. When the drug is used in the larger doses, which seem to be necessary, it is advisable to restrict the activities of the patient to his bed and keep him under very careful observation. In the editor's practice, the drug is administered as follows: The first day, 20 grains (1.3 Gm.) every 15 minutes for 4 doses is given. If there is no particular reaction, this dosage is repeated on the second day and thereafter for a week or two longer, it is given in 10- or 20-grain (0.6 or 1.3 Gm.) doses 4 times daily. Usually the acute discharge will disappear in 72 hours and there will be little, if any, discharge at the end of 10 days if the drug is going to prove efficacious. At the end of this period the patient is carefully examined for discharge and organisms. Whether they are found or not, the procedure is completely repeated after a few days' rest. Following this treatment excellent results have been obtained in a goodly number of acute gonorrheas.

The above treatment is fairly mild and C. P. Mathe and A. Spitalny⁸ use much larger doses, although their plan is in general like the above. These writers like to give approximately 120 grains (7.8 Gm.) a day for 2 days and then to establish a high maintenance dosage. They also feel that if no beneficial results are obtained in 7 to 10 days the treatment should be discontinued and other forms of treatment substituted. Mathe calls attention to the fact that there are recurrences after the treatment has been discontinued but believes that there are few, if any, contraindications to its use. One should avoid the use of the drug in patients who are anemic, or who have impaired renal or liver function. When evidence of *toxic effects* are observed the drug should be discontinued and *fluids should be forced*. *Methylene blue* is supposed to be of value in de-

creasing the severity of methemoglobinemia in patients showing sensitiveness to the drug.

J. I. Farrell, Y. Lyman, and C. P. Youmans⁹ treated 10 cases of gonorrheal urethritis with sulfanilamide by mouth and only 5 of the patients responded. The other 5 deriving little apparent benefit from the drug were also treated by local therapy. None of the 10 patients developed posterior urethritis, prostatitis or epididymitis. It seems likely that the presence of the sulfanilamide in the urine and prostatic tissues is directly responsible for the lack of the unpleasant complications of anterior gonococcic urethritis and to determine this point several experiments were made with dogs and the following conclusions were drawn: When the kidney is normal the drug is excreted in concentrations that are bactericidal, thus the lower urinary tract is continually in contact with a strong bactericidal urine. The prostatic secretions are equally bactericidal. The infection therefore is prevented in the posterior urethra, thus eliminating the possibility of complications. The drug must be given in adequate amounts.

J. E. Heslin and W. A. Milner¹⁰ have been treating gonorrhea *locally* with the **arsphenamines**. Neoarsphenamine and sulfarsphenamine are presented for the first time as local agents in the treatment of gonorrheal urethritis. The ability of these drugs to control symptoms protects the patient and others, as well as lessening the danger of complications. In non-specific urethritis due to staphylococcus infection, the action of these drugs is most rapid. Although we realize the arsenicals are not "specific" for the disease, in our hands they have proven far more efficacious than any other drug. **Sulfarsphenamine**— $1\frac{1}{2}$ grains (1 deci-

gram) to 1 dram (4 cc.) of distilled water—is the solution recommended.

The treatment of *gonorrheal vulvovaginitis* in children has always presented a difficult problem. **Sulfanilamide** seems to be fairly efficient in these cases and children seem to tolerate the drug even better than adults. S. J. Hoffman, M. Schneider, M. L. Blatt and R. D. Herrold¹¹ treated a series of 25 patients with the following results. Seven were cured in an average of 17.3 days and 9 in an average of 42.9 days. Only 2 of the 9 remaining patients were cured by additional administration of the drug. A standard dose of sulfanilamide was used in all; the results suggest the comparative futility of the continuation of more than 2 standard courses of treatment. The dosage used in general is 15 grains (1 Gm.) daily to 20 pounds (9 kg.) of body weight given in divided doses at 6-hour intervals. After 2 days this dosage is gradually diminished throughout the balance of the treatment.

Criteria of Cure: When is gonorrhea cured? From the Central Gonorrhea Clinic, Bureau of Social Hygiene, Department of Health, City of New York, comes the following communication by M. Wishengrad¹² concerning the tests for determining the cure of gonorrhea. In the future, no case under treatment for gonorrhea (this applies to male cases) shall be discharged as cured until the following tests have been made and unless the results of such tests are uniformly satisfactory. Before the tests are begun, urines must be clear and the discharge must have stopped at least 7 days.

1. We endeavor to test the patient's reaction by passing a sound large enough to pass the meatus comfortably. The sound must not pass the cut-off muscle into the posterior urethra. Slight movement of the sound back and forth 2 or 3 times should be attempted. The patient

is to be given a glass slide on which to place any urethral secretion which may occur at any time until the next visit.

2. If no reaction, such as recurrence of discharge, occurs within 4 days, massage the prostate and examine the secretion for pus and gonococci.

3. If no gonococci are found (and not sooner than 4 days after prostatic massage), instill 15 to 30 minims (1 to 2 cc) of 1 per cent silver nitrate into the posterior urethra with the aid of the Keyes-Ultzman syringe. Give patient a glass slide on which to collect any secretion that may result from this procedure. The patient returns the following day and if no untoward reaction occurs following the instillation, massage the prostate and examine the secretion for pus and gonococci.

4. If all of the above tests produce no discharge and the examinations reveal no gonococci in any secretions, instruct the patient to drink some beer or alcohol and return in a week. If no reaction occurs, instruct the patient that if he indulges in intercourse he must use a condom. If all tests thus far are negative, the patient can be discharged with the admonition that condoms be used during intercourse for a minimum period of 3 months to protect both himself and his sex partner.

It is understood that the above sequence obtains only in those cases that give satisfactory results with each of the tests. In the event that any 1 test produces a recurrence of discharge and the gonococci are discovered in this discharge, the sequence is, perforce, interrupted. The patient may, at this point, require further instillations or irrigations for the discharge. Again if the prostatic massage reveals the gonococcus, then, of course, we institute a series of prostatic massages until the gonococcus can no longer be discovered in at least 3 suc-

cessive smears. When such untoward reaction occurs, the entire series of tests must be applied from the beginning.

KIDNEY

Nephrosis

Nephrosis, so-called, is usually accompanied by crippling edema even though the kidney is not irreparably damaged and even though in those cases where the excretion of water is greatly disturbed there is usually good renal function as proven by routine tests. On the hypothesis that the disease is a metabolic disturbance involving the thyroid, thyroxine and thyroid extract have been given with promising results. High protein diets have been fairly successful, although none of the explanations of the disease nor any of the treatments have been entirely satisfactory.

Treatment—Because of the loss of serum albumin and of its possible significance in reducing the water excretion, many substances have been injected into the blood stream in an attempt to increase its power to hold water and to remove it from the tissues. Among these have been hypertonic solutions of *dextrose* and of *sucrose*, *solutions of acacia*, *whole blood*, and *hypertonic salt solution*. Although some help has been obtained from these agents, not one of them has proved uniformly and continuously successful.

As a result of the observation that at times transfusion sometimes created a marked diuresis, C. A. Aldrich, Joseph Stokes, Jr., W. P. Killingsworth and A. C. McGuinness¹³ decided to treat some of these cases of marked nephrosis plus general anasarca with intravenous injections of *human lyophile serum*. The serum was administered according to the following technic. The lyo-

phile serum is distributed in sterile bottles marked as to the number of cubic centimeters of serum from which the dried powder was derived. It had previously been found that this powder could be dissolved in one-fourth its original volume of distilled water. This was the concentration used in our first cases. Later it was found that the same amount of compatible blood serum would dissolve the powder, so that a concentration of 5 times could be used. This made a thick, honey-like, syrupy solution, which could be injected directly with little difficulty by means of what we designate in our hospitals as a "scalp transfusion" set or with a simple 30 or 50 cc Luer syringe. The size of the needle used depended on the caliber of the patient's vein, a 20 or a 22 gauge needle usually being satisfactory. Occasionally, owing to the massive edema present, it was necessary to cut down on either the great saphenous vein at the ankle or on one of the veins in the cubital fossa. However, the superficial jugular vein may be used safely.

The concentrated serum was injected slowly, not more than 5 cc a minute. When a reaction occurred with the first dose of serum, all subsequent injections contained from 3 to 5 minims (0.19 to 0.3 cc) of solution of 1/1000 epinephrine hydrochloride. It is necessary to state here that care must be exercised to prevent this concentrated serum from escaping into the tissues, as it is quite painful, causing rapid and intense local swelling at a site at which it is spilled. The serum when accidentally injected into the tissues caused no necrosis or slough. Venous thrombosis did not follow the injections.

Because there are often large fat globules in the lyophile serum, it is safer to pass it through a coarse filter (Berkefeld N) to prevent the possibility

of fat embolism. All serum should be freshly prepared with distilled water or compatible serum and used immediately.

It was felt that until the proper dose was determined by experience it would be safer to use frequent small injections. Accordingly, we did not in this series exceed 2 2/3 ounces (80 cc.) or the equivalent of about 10 2/3 ounces (320 cc.) of normal serum. It was noted that even this small amount apparently induced diuresis in some of the patients.

Nine patients with the disease were thus treated and complete immediate diuresis immediately took place. Delayed and incomplete diuresis occurred in 1 patient while in 2 patients no results were obtainable.

Hypertensive Disease

Treatment—During the past few years the urologist has been confronted with the problem of hypertensive disease. Observing authorities have attempted to cure so-called essential hypertension by adrenal sympathectomy (Crile), renal sympathectomy (Hess, Miliken, etc.) and various other operations upon the lumbar sympathetic nervous system. Results with all of these procedures have been very unsatisfactory. It has long been observed that hypertension is associated with certain types of renal disease. Goldblatt and his associates have shown that an ischemic kidney from any cause is a direct stimulant to increased blood pressure as a result of some substance elaborated by the impoverished cells stimulating the adrenal cortical hormone. If this theory were correct, the removal of a kidney definitely known to be ischemic for one reason or another should result in relieving, if not completely curing, certain types of hypertension. W. F. Leadbetter and C. E. Burkland¹⁴ report the apparent cure of a colored boy, 5 1/2 years old, with marked

hypertension of 3 years' standing by the removal of such an ischemic ectopic kidney, the main artery of which was partially occluded.

C H Boyd and L G. Lewis¹⁵ report a patient, aged 31, with malignant hypertension due to arterial disease of the right kidney. **Nephrectomy** was followed by clinical cure of the hypertension. At the time of operation in September, 1937, the blood pressure was 210/130 and on March 20, 1938, the blood pressure was 124/84. As a result of the experiments of Goldblatt and others, diagnostic studies must be perfected in cases of hypertension so that unilateral arterial disease may be more readily diagnosed.

Pyelonephritis

One of the commonest of kidney infections is that known as acute and chronic pyelonephritis. The acute condition manifests itself by high fever, sweats, pain in the loin, rapid pulse and the accompanying frequency, urgency and straining in urination. This condition is usually erroneously called pyelitis, but it is difficult to believe that such an acute condition is not usually an exacerbation of a chronic pyelonephritis and is brought on by some sudden ureteral obstructive lesion or by an overwhelming infection. As a rule the acute condition subsides and a chronic bilateral pyelonephritis remains. There are many cases of chronic pyelonephritis that are often mistaken for chronic glomerulonephritis and a differential diagnosis is very important. In the early stages of pyelonephritis the blood pressure is usually within normal limits but as the disease progresses the blood pressure may rise. The eyegrounds are perfectly normal in pyelonephritis, on the other hand, glomerulonephritis is the only variety in which retinitis is common. This is ordi-

narily designated as an albuminuric retinitis; it is characterized by anemia and edema of the disc; generalized, rather dense edema of the retina, usually grayish white, hemorrhages and cotton wool patches, and, in the macular region, the radiating star figure made up of large, thick groups of hard white exudate. This picture is never found with uncomplicated obstructive lesions of the urinary tract, although the 2 disease entities may exist in the same patient.

The urine in cases of pyelonephritis is slightly cloudy and frequency shows the slight opalescence associated with bacteriuria. The specific gravity is usually low, there may be some albumin and many leukocytes and in old chronic cases only a very small number of the latter may be found. Bacteria, however, are usually plentiful. With regard to the urine, the most helpful fact in distinguishing pyelonephritis from chronic glomerulonephritis is that with the former casts are rare and erythrocytes are only occasionally found. The leukocyte count is usually higher in pyelonephritis.

Obstruction of that part of the urinary passage which lies below the bladder results most frequently from prostatic hypertrophy, carcinoma, contracture of the neck of the bladder or urethral stricture. Any of these may cause retention of urine, back pressure and renal insufficiency. Due to back pressure in these conditions there is dilatation of the pelvis and calyces, thinning of the renal cortex and impairment of function, and at times more or less uremia. These conditions are sometimes diagnosed as glomerulonephritis.

Very often the clinical picture of impaired renal function, hypertension and hematuria in cases of polycystic disease is very similar to the symptoms associated with chronic glomerulonephritis. There are symptoms of gastrointestinal

disorders, anemia, headache and weakness. Examination of the urine will reveal a low specific gravity, albumin and erythrocytes. There is, too, a definite impairment of renal function.

Hyperparathyroidism with disturbances of calcium and phosphorous metabolism and the formation of stones in the urinary tract may present a clinical picture that is very often mistaken for glomerulonephritis. Water intoxication must be considered. It in itself will cause symptoms of uremia, restlessness, asthenia, nausea, convulsions, coma and at times oliguria. On the other hand, surprisingly large amounts of water may be taken if the output is satisfactory.

Chronic glomerulonephritis, of course, is considered a disease that is virtually incurable, although the life of the patient may be prolonged for indefinite periods, while the conditions for which it is usually confused, for the most part, are curable entities and it should be a rule that where there is even the slightest doubt as to the diagnosis the patient should be given the benefit of a complete urological investigation. If this is thoroughly carried out a small but definite group of patients whose condition has been diagnosed as chronic glomerulonephritis will be found to have conditions that can be partially or completely relieved. A. J. Scholl.¹⁶

In the Guiteras Lecture before the American Urological Association last year, W. F. Braasch,¹⁷ in discussing the clinical data concerning chronic pyelonephritis, summed up our present day information in the following manner:

A working knowledge of the bacteriology concerned in infection of the urinary tract is essential to its intelligent treatment.

Although, with renal infection, some bacteria may cause clinical and pathologic signs which are characteristic, any of the

various bacteria may cause the complications and pathologic changes which may occur.

Although pathologic changes resulting from various types of bacteria are in general similar, infection with *Aerogenes* and *Proteus* is often more resistant to therapy and often causes more widespread involvement of the submucosal tissues than does infection with other bacteria.

Although all bacteria may cause mild symptoms and but little deformity, yet this type of infection is observed relatively more often in the presence of cocci than of other bacteria.

Mixed infection may occur and often requires persistent and intelligent treatment in order to eradicate the various types of bacteria.

Amicrobic pyuria is present in more than 20 per cent of cases of chronic pyelonephritis. Although a specific organism may be present in some cases, in most cases the bacteria have become so indolent and scattered that they fail to appear in cultures. Anaerobic bacteria are only occasionally of etiologic importance.

The pH of the urine is not of much diagnostic importance in renal infection unless it is distinctly on the alkaline side. Knowledge and adjustment of it is, however, essential to intelligent treatment with mandelic acid and in ketogenic therapy and to a less extent to other forms of chemotherapy.

Lithiasis secondary to chronic pyelonephritis is a distinct type of renal lithiasis. It occurred in 5 per cent of a series of cases encountered at the Mayo Clinic. It is attended by roentgenographic signs which may be characteristic. Its origin is apparently not the result of the urea splitting action of bacteria, since the pH is usually in the range of neutrality. It causes comparatively few renal symptoms.

or complications in most cases and usually does not affect the course of the infection over a period of years. All types of bacteria may be concerned.

Renal hematuria secondary to pyelonephritis occurs in 12 per cent of cases; it is usually a late complication and is caused by granulomas or areas of superficial ulceration in the mucosa of either the pelvis or ureter, very often in the latter. It often can be stopped by controlling the infection with chemotherapy or by means of pelvic lavage. Its occurrence is apparently not related to the species of bacteria or to the pH of the urine. All types of bacteria are concerned, although in the majority of cases *Aerogenes* and colon bacilli are present.

Urographic deformity which accompanies chronic pyelonephritis and which is regarded as characteristic, consists of caliectasis and ureterectasis with cicatricial narrowing of the infundibula and of the renal pelvis. The outline of the dilated calix is usually more irregular in the presence of infection than in the presence of obstruction. The dilatation of both ureter and calices usually is adynamic in character. On the other hand, pyelectasis, which is of comparatively infrequent occurrence, is likely to be the result of obstruction. Dilatation of the ureter is usually of greater diagnostic importance than that observed in the calices. Adynamic or atonic ureterectasis may be explained by periureteritis affecting the trophic nerves which supply the ureteral wall. In view of the marked ureterectasis and angulation of the ureter so frequently observed, it is noteworthy how seldom actual constriction of the ureter is found. The degree of deformity is not necessarily dependent on the duration or the degree of infection, but more on the extent of submucosal invasion. Although all types of bacteria are concerned, less deformity usually is seen in

the presence of coccal infection than in the presence of infection with other bacteria. The greatest deformity is observed when the infecting organisms are *Aerogenes* or *Proteus*. The excretory urogram often is misleading in that it fails to visualize the deformity in the calices and in the ureter.

Treatment—Removal of foci of infection in cases of chronic pyelonephritis is not so efficacious as it is in cases of acute infection. Such foci may have a direct bearing on persistent prostatic infection, and should be **removed**. Prostatic infection often prevents eradication of pyelonephritis and requires specific treatment. **Sulfanilamide** promises to be a valuable adjunct to prostatic treatment.

Nephroptosis is seldom a factor in causing chronic pyelonephritis. When renal stasis is present it is usually recognized by clinical and urographic signs and **surgical intervention** may be necessary. However, such intervention is required in only a small proportion of cases of chronic pyelonephritis.

Since recovery from chronic pyelonephritis is spontaneous in fully 20 per cent of cases, too much credit must not be assumed for various methods of treatment which have been employed.

It is surprising how seldom complications which require surgical operation appear. Surgical treatment usually is not indicated unless one of the following is present: Some form of obstruction; localized, persistent infection; destruction of renal function, or atrophy. Such treatment was found necessary in but 3 per cent of the 526 cases of chronic pyelonephritis observed at the clinic in the past 7 years.

In the recent developments of chemotherapy, compounds have been produced which have given startling results. I refer particularly to **sulfanilamide** and

mandelic acid. Although sulfanilamide gives promise of being a potent factor in eradicating renal infection in many cases, in common with other similar drugs, it is of greater value against acute than against chronic infection. There is a vast difference in the results obtained in treatment of chronic and of recent renal infection. Although most renal infections, when acute, subacute, or recurring, can be controlled by recently developed chemotherapy, nevertheless when the infection becomes chronic, secondary and anatomic changes often will defy all treatment.

Eradication of chronic pyelonephritis will be possible by prophylaxis and by thorough, intelligent treatment of acute and subacute infection. Treatment of urinary infection still demands the intelligent supervision of the urologist

The Nephrectomized Patient

C L Denning,¹⁸ in discussing the medical future of the unilaterally nephrectomized patient calls our attention to the fact that the expectancy of life of the unilaterally nephrectomized person depends (a) On the cause for which the kidney was removed; (b) on the condition of the remaining kidney, and (c) on the social status of the individual. Certain operative procedures applicable to tuberculous and pyogenic cases are available which diminish the mortality and shorten the postoperative course. Control of the pyogenic infection of the remaining kidney is an ambition worthy of effort. The young person whose kidney has been removed for other causes than malignancy has a normal expectancy of life. Marriage is permissible for these individuals who have a normally functioning kidney after a reasonable length of time following nephrectomy. Pregnancy is permitted for all those healthy individuals who have

not had a malignancy. Although the problem of malignancy is a baffling one, we, as urologists, may find a source of satisfaction in our treatment of lesions requiring a nephrectomy in a statement from the Association of Life Insurance Directors, namely, that the death rates for nephrectomy were lower and the expectancy of life greater than was anticipated.

Renal Mobility

The normal kidney is a very movable organ. This has been recognized for years but only recently has the study of renal mobility lent itself advantageously for diagnostic purposes. We have long known that a kidney could be movable, palpable and ptosed without causing symptoms or being the seat of pathological changes. The location of the normal kidney in the supine position is higher than when the patient is in the erect position. Serial pyelograms have shown variations in the position of the kidney in the same individual and these have also been noted in postural changes.

In association with Dr Ralph Bacon and Dr B Swayne Putts, Elmer Hess¹⁹ reports a technic and some interesting results in a new method of studying variations in renal position. This decreases the expense of serial films and has made comparative study of kidney movement much simpler. It is called respiration pyelography.

Technic—With the catheters in place first take a plain roentgenogram followed by a plain pyelogram with the patient simply holding his breath, after which a third film is used with a fast cassette. The patient is now instructed to take a long breath and hold it and the first exposure is made. The patient is then instructed to exhale completely and remain quiet while the second exposure is made on the same plate. These pyelograms are all made in the supine position.

The taking of 2 pictures on the same film, 1 in deep inspiration and 1 in deep expiration, has proven of great value in the following conditions:

1. It helps to rule out so-called non-pathological ureteral kinks.

2. It has established, for all practical purposes, normal renal motion.

3. It is of important significance in the differential diagnosis of perinephric and subdiaphragmatic abscess. In perinephric abscess there is very limited motion on the involved side with normal diaphragmatic motion. This limitation of motion occurs early in the disease and in subdiaphragmatic abscess there is limited motion on the diseased side with fixation of the diaphragm.

4. It is a valuable guide, postoperatively, after any surgical procedure used for the fixation of nephroptotic kidneys with kinked ureters. In these cases the operated kidney is fixed and moves but slowly in both deep inspiration and deep expiration as compared to its unoperated fellow.

5. It is of some prognostic value in certain other renal conditions and is a distinct aid in planning operations upon kidneys, the seat of calculous disease, pyonephrosis and tumor. For example, if the diseased process is limited to the kidney itself there should be normal range of motion on deep inspiration and deep expiration. If, on the other hand, the kidney is fixed, it is *prima facie* evidence that the pathologic process, whether it be infection or tumor, has spread beyond the confines of the capsule. In the latter, of course, the prognosis is not as favorable as where such extension has not taken place and again the surgical approach will be more thoughtfully planned if surrounding renal structures are designated by the respiration pyelogram, to be involved. A nephrectomy with perirenal fixation is a far more for-

midable procedure than is one where this fixation does not exist.

6. The procedure is also useful in hydronephrosis in suggesting whether or not the probable cause of the nephrosis may or may not be an aberrant vessel. The procedure and technic are simple, easy and inexpensive, and will be of great value to those choosing to use it.

PROSTATE

Hormonal Therapy—For the past few years efforts have been made on the part of many clinicians to treat hypertrophies of the prostate by hormones. As early as 1889 Brown-Sequard was one of the first workers to advance the theory that the testicles manufactured an internal secretion. Lower and his associates used *inhibin*, a testicular hormone, which they believed had an inhibitory effect upon the pituitary gland. They treated a large series of simple hypertrophies of the prostate with inhibin and while some of their results seem encouraging many of their cases required surgical extirpation later. Their patients received the equivalent of 2 ounces (60 Gm.) of fresh testes for 3 months and then a maintenance dose of $\frac{2}{3}$ ounce (20 Gm.) was advised daily. About 65 per cent of their cases they considered improved. H. W. E. Walther and R. M. Willoughby²⁰ have treated 15 patients with male sex hormone preparations and noticed definite clinical improvement. They believe that in early prostatism or where, for some serious physical disability in any type of prostatic obstruction, surgery seems inadvisable, the newer male sex hormones should be given a thorough trial. They stress the disadvantage of being obliged to use a continual maintenance dose. They use androsterone and testosterone propionate for oral and intramuscular use.

J. G. Strohm, Z. C. Edelson and G. H. Merryman²¹ use *testosterone* and report their results as fair in early prostatic hypertrophy, with partial results in moderate hypertrophy, and poor results in long-standing hypertrophy. They suggest that with the use of the hormones, massage of the gland be employed. Subjectively, their patients seemed to obtain great relief from their symptoms without much change being noticed in the size of the gland.

A. Oberholtzer²² comes to approximately the same conclusion after a careful study of 34 patients, claiming 27 favorable results against 7 negative ones. Stressing the fact that under this form of treatment one cannot obtain reduction in the volume of the prostate and that if the therapy fails, surgical intervention is by no means endangered, and that in his experience these patients stand prostatectomy with fewer complications. He uses $1\frac{1}{2}$ to $1\frac{1}{8}$ gram (5 to 10 mg.) per day injected intramuscularly of testosterone propionate.

It would seem to be advantageous for the urologist in certain selected groups of cases to try these substances, but a great deal more experimental work and clinical observation of the actions of these substances must be made available before the treatment can be properly evaluated. At the present time the treatment is empirical and cannot be considered as yet to be upon a completely rational scientific basis. The mechanical removal of the obstructing prostate is at the present time the only hope for the relief of prostatism.

Transurethral Prostatectomy—Sufficient time has elapsed since the first transurethral procedures were advocated to properly evaluate this operation. Its dangers are still sepsis and hemorrhage, both of which are reduced to a minimum as the individual operator gains in ex-

perience. That accidents still occur during transurethral procedures is obvious, that patients still occasionally die from both hemorrhage and sepsis is still true. However, it is admitted by most men having much experience with this procedure that perhaps it is indicated as the best treatment in obstructive carcinomas of the prostate.

G. J. Thompson and J. L. Emmett²³ have studied 107 original cases of carcinoma, a total of 17 have thus far obtained at least a 4-year cure, while 10 patients are still surviving in the 5- and 6-year period after operation. In all of these cases transurethral operation was done in order to relieve urinary obstruction and the only hope was to relieve symptoms.

D. Schlapik,²⁴ in reporting his work in 471 patients, is convinced that the suprapubic operation should be reserved for massive prostates but that the average prostatic obstruction can be relieved by resection. Postoperatively he irrigates the bladder every half hour for 12 hours and then every hour the second 12 hours. The second 24 hours the patient is irrigated every 2 hours. The frequency of irrigation is increased if bleeding starts at any time. The catheter is allowed to remain in place for 24 hours after the temperature is normal.

C. W. Collings²⁵ pleads for early transurethral resection, stating that most types of obstruction of the bladder neck, if the patient heeds the beginning symptoms of prostatism, can be relieved by transurethral surgery long before permanent damage has occurred to the heart and kidneys.

It must be emphasized that this is an operation for experts and, as Alcock says, the type of operation for prostatic obstruction depends more upon the operator than upon anything else. To paraphrase him, "Young should do a

prostatectomy, I should do transurethral surgery." This is also true of most surgeons and surgical procedures. The operator should do the procedure with which he is most familiar and should use the method which gives him the best results. A few years ago Gideon Timberlake advocated the use of the resectoscope in the treatment of prostatic abscess. He demonstrated that it was a simple matter with the cutting loop to slice a window from the prostatic urethra, enter the abscess pocket and that quick, easy evacuation was accomplished with splendid healing results. This technic has been used by Thompson and others.

R. Bell²⁶ reports that most prostatic obstructions thus treated may be permitted to leave the hospital within a few days in good general condition. The work is done with very little shock and the operation is neither formidable nor is it followed by complications that may occur when the abscess was drained by the perineal or suprapubic route.

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THERAPEUTICS, GENERAL

Edited by E. A. DAUGHERTY, M.D.

ACTIVATED CHARCOAL

Due to the lack of a well-defined plan of treatment for a patient suffering from an overdose of phenolphthalein, B. Fantus and J. M. Dyniewicz¹ studied experimentally the practical value of charcoal for this purpose.

The following doses of phenolphthalein was taken by 10 volunteers at intervals of a week:

Dose 1—0.30 Gm of phenolphthalein.

Dose 2—Dose 1 followed in 15 minutes by 15 Gm of magnesium sulfate.

Dose 3—Dose 1 followed in 15 minutes by 15 cc. of castor oil

Dose 4—Dose 1 followed in 15 minutes by 7.5 Gm of activated charcoal. In cases 1, 2 and 3, 15 Gm of charcoal was given

Dose 5—Dose 1 followed in 15 minutes by 7.5 Gm (15 Gm in cases 1, 2, and 3) of activated charcoal and followed 15 minutes later by 15 cc of castor oil

Dose 6—Same as dose 1

The results showed that, while there was considerable variation in total percentage of phenolphthalein eliminated in relation to that ingested (average 3.3 per cent), there was a consistent and marked diminution in the elimination following the administration of activated charcoal, the elimination figure averaging 1.4 per cent, the controls averaging more than twice this amount. The authors concluded from the results of their experimental study that, in case an overdose of phenolphthalein is taken, there be administered as soon as possible at least 25 times—or as large a quantity as one can get the patient to take—of activated charcoal diffused through water. The authors recommend for the sake of palatability that the charcoal be taken in ginger ale or "Coca-Cola." It may be

taken in divided doses. An excess of charcoal is harmless. In un-co-operative patients one would be justified in passing the stomach tube to administer the charcoal if the patient refuses to swallow it. In cases where an exceedingly large quantity of phenolphthalein has been taken, it might be advisable to follow the activated charcoal by a tablespoonful of castor oil

ALUMINUM HYDROXIDE GEL

Therapeutics—E. S. Emery, Jr., and R. B. Rutherford² report on the use of colloidal aluminum hydroxide in the treatment of 12 cases of peptic ulcer. Eight of the 12 cases were considered to be of a severe type, and 4 were of a more moderate type. The drip method of administration of the gel was used in 5 cases and the oral method in 7 cases. After the first week all patients were treated by the oral method. The aluminum hydroxide gel was used in a concentration of 1 part of gel to 3 parts of water. When using the drip approximately 15 drops of the solution per minute was given through the tube. Orally, the solution was administered in 60 cc doses hourly, from 8 A. M. to 9 P. M. The patients in addition were fed on a Sippy diet.

The results show that all patients were relieved of their pain within 24 hours and had no recurrence of pain while remaining on treatment.

Colloidal aluminum hydroxide in addition to neutralizing the secreted acid, decreases the titratable acidity of the gastric juice.

The drug is absorbed but slightly, and does not interfere with the acid base balance. The authors recommend that all ulcer patients who fail to respond satisfactorily to the Sippy regimen should be treated with aluminum hydroxide before surgical intervention is carried out.

ANTIPYRIN

Therapeutics — Antipyrin has been used for many years in the treatment of rheumatism, and many men consider it equally as effective in this condition as the salicylates. L. Bouchut and M. Levrat³ reported very good results with the use of antipyrin in a series of cases which they studied. The authors did not observe any disturbance of digestion or impaired kidney function attributable to the use of the drug in their cases, and they give as their indications for its use: (a) Cases of acute articular rheumatism with persistently high temperature, (b) cases in which salicylates are badly tolerated or fail to produce satisfactory results, and (c) rheumatic carditis, for which they consider antipyrin specific.

BEE VENOM (APICOSAN)

Therapeutics — J. Kroner, R. M. Lintz, M. Tyndall, L. Anderson and E. E. Nicholls⁴ report on the use of bee venom (apicosan) in the treatment of 100 patients with rheumatoid arthritis. Of the patients treated 73 showed definite improvement, as indicated by a fall in the corrected sedimentation index, and an alleviation of the clinical symptoms. Seventeen were free from symptoms 6 months to a year after the treatments were discontinued, 18 had only mild transitory pains, and 38 had moderate improvement.

Ten patients had an advanced, active deforming type of arthritis. Six of these

patients improved with an average of 31.5 injections of bee venom.

In patients with moderately severe arthritis, the range of injections was from 6 to 48 and in patients with a mild arthritis, from 6 to 38.

Dosage and Administration — All injections were given intradermally. The site selected depended on the location of the most painful joints. The skin was cleansed with alcohol and wiped dry with benzene. The treatments were continued at weekly or biweekly intervals, increasing 0.1 cc. at each visit. Only 0.1 cc. was put into a wheal and the wheals were placed about 1 inch apart. When a patient had received 0.5 cc. of concentration I, he was given 0.1 cc. of concentration II, which was increased to 0.5 cc. and then concentration III was started. The dose was then increased 0.1 cc. at each visit until the patient was receiving 1 ampule of concentration III. The development of large pseudopodia at the site of injection denoted sensitivity and the dose was not increased for several visits.

BENZEDRINE SULFATE (BENZYL METHYL CARBINAMINE, AMPHETAMINE)

Therapeutics — A series of 28 patients admitted to the Syracuse Psychopathic Hospital in psychotic states brought on by alcohol were treated and the results reported by E. C. Reifenstein, Jr., and E. Davidoff.⁵ The series included 15 patients with pathologic intoxication, 5 with delirium tremens, 4 with acute hallucinosis and 4 with Korsakoff's syndrome. The authors report a definite and at times a marked acceleration in improvement in 93 per cent of their cases. In cases of delirium tremens the results with benzedrine were equally as good as

those obtained with spinal fluid drainage. With the exception of 2 patients with Korsakoff's psychosis complicated by arteriosclerosis, none treated thus far with benzedrine sulfate have required commitment to a hospital for chronic mental patients. According to the authors, in states of intoxication with alcohol in which no psychosis was demonstrable benzedrine sulfate usually produced an even more satisfactory response than in states of intoxication in which a psychosis existed. Five to 10 mg of benzedrine sulfate in the morning caused a rapid disappearance of the headache, fatigue and mental depression which usually follows an alcoholic debauch.

In the psychotic patients 10 to 30 mg daily by mouth was the usual dose of benzedrine sulfate. In a few cases the drug was administered intravenously in 10 to 30 mg. doses.

Toxic Effects—S. P. Waud⁶ discusses the effect of toxic doses of benzyl methyl carbimamine in man. The subject used in these experiments was a normal man, aged 27, weighing 97 Kg. In all there were 8 separate experiments carried out varying from 7 to 10 days apart. In each experiment 2 new benzedrine inhalers were used simultaneously and were inhaled normally and at times deeply for periods of from 4 to 6 hours continuously. It was calculated that approximately 650 mg (10 grams) was inhaled in each experiment (6.7 mg per Kg of body weight). The estimated absorbed doses was believed to be approximately 400 to 500 mg.

This would be approximately 50 times the usual therapeutic dosage of benzedrine sulfate by mouth; it is about 1000 times the usual therapeutic dosage of the inhaler 2 inhalations an hour.

The conclusions drawn by the author regarding the toxic effects of benzedrine are as follows:

1 Continuous inhalation of benzedrine can produce definite toxic effects characteristic of sympathomimetic excitation, stimulation of the central nervous system and depression of the cardiac muscle.

2. Ephedrine and benzedrine are pharmacologically very similar in toxic doses.

3 Benzedrine in toxic doses reduces libido moderately after sympathetic stimulation subsides.

4 The pressor effect of benzedrine is marked, but relatively temporary.

5. Benzedrine in toxic doses is a diuretic in normal individuals.

6 The stimulation of the central nervous system is marked, but relatively temporary and is always followed by marked fatigue and mental depression when toxic doses of benzedrine are absorbed.

7 Permanent organic changes are probably negligible with normal doses of benzedrine over long periods of time.

8 The margin of safety of benzedrine is great in normal persons.

9. The likelihood of addiction is quite possible.

10 The indiscriminate use of benzedrine is very unwise.

CALCIUM

Therapeutics—H. Taege⁷ reports on the therapeutic use of calcium in lead poisoning. The author has observed a calcium deficiency in the erythrocytes of patients with lead poisoning and, in order to re-establish normal conditions, the administration of calcium is necessary. However, due to the mobilizing effect of calcium on the lead in the body, the administration of calcium must be carried out with great caution.

In the presence of severe symptoms of intoxication, all measures that mobilize lead are strictly contraindicated. After the acute symptoms of intoxication have subsided, then calcium should be given in small doses to compensate for the calcium deficiency. Large doses, according to the author, are contraindicated. Milk, and phosphates in a suitable ratio, should be given in gradually increasing doses.

The daily quantity of milk should not exceed 1 liter. Later, small doses of calcium gluconate may be given by mouth. The author advises against the use of calcium intravenously in cases of lead poisoning.

R. S. Lampson and F. A. Simeone⁵ report on their clinical investigation of the use of calcium chloride in the relief of colic-like pain and in spasm of the bladder. In 14 cases treated with intravenous injections of calcium chloride, symptomatic relief was obtained in all but 2, in both of which large doses of morphine was the only drug that gave relief from the pain. The drug appears to be effective in those cases of spasmodic pain resulting from a localized irritative state.

The drug is also useful as a diagnostic aid in that, with the prompt relief of pain, the marked voluntary muscular spasm which accompanied the pain is relaxed. This permits more careful examination of the patient without resorting to the use of morphine with its accompanying generalized sensory depression.

CARBON MONOXIDE

Chronic Toxic Manifestations Due to Prolonged Exposure—H. G. Beck and G. M. Suter⁹ report on the frequency with which cardiac symptoms appeared in patients whose illness was definitely due to frequent and prolonged exposure to carbon monoxide gas.

The injurious action of carbon monoxide gas is due indirectly to its unusual affinity for hemoglobin, causing the oxyhemoglobin molecule to be replaced by carbon monoxide, thus producing a state of anoxemia. Structures endowed with a rich blood supply, such as the myocardium and the central nervous system, show relatively more damage in states of

anoxemia than tissues with a less abundant blood supply.

The present series reported consists of a study of 136 cases of chronic carbon monoxide poisoning extending over a period of 15 years.

The lesions affecting the heart, brain and other organs are primarily vascular, consisting of small hemorrhages and perivascular infiltration with local necrosis. When the heart is affected, coronary thrombosis frequently develops.

Patients who appear to recover from acute asphyxiation frequently have later manifestations, which appear in 3 to 7 days. These delayed symptoms may affect the heart, brain or other organs and terminate fatally.

Those who survive the delayed manifestations may recover completely or finally may have severe organic disease of the heart or other organs, to which they finally succumb.

CARBON TETRACHLORIDE

Poisoning—A case of poisoning with very good clinical evidence of injury to the liver from inhalation of the vapor of carbon tetrachloride is reported on by G. F. Madding and H. R. Butt¹⁰. Although carbon tetrachloride has been a standard drug in the production of experimental hepatitis in animals, few clinical cases have been encountered, and according to the authors the case reported is the only one in the records of the Clinic.

The patient, a Russian man, aged 24 years, had been employed at a dry cleaning establishment for the past 5 years. The cleaning agent used was carbon tetrachloride and the patient had been exposed constantly to small quantities of this without apparent untoward effect until 1 month prior to admission, when he commenced to feel bad.

The first symptoms complained of was a dull ache in the region of the kidneys, associated with dysuria and slight nocturia. Erythrocytes were found in the urine. There was also present a constant, dull aching across the upper portion of the abdomen, an associated distress around the heart and marked lassitude. Finally, when exposed to the fumes he suffered severe headaches, dizziness, and nausea and vomiting. He gave up work 1 week before admission to the Mayo Clinic, and all symptoms abated except extreme lethargy about which he was much concerned. The important physical findings were an obese man with a pale pasty complexion. The liver was palpable to the level of the umbilicus on the right, was tender, indurated and rough. The tip of the spleen was also palpable but not tender. No ascites or dilatation of superficial veins. Albumin was present in the urine, grade 2. The bromsulfalein test of liver function showed retention of dye, grade 2.

Treatment -- The patient was instructed to stop work, given a diet high in carbohydrate, low in fat and low in protein. In addition to the diet the patient ingested nearly 2 gallons (4000 cc) of Karo corn syrup in a 7 weeks' period between his first and second visit to the clinic. At the time of the second visit he appeared to be in good health, was free from symptoms and had gained 7 pounds. A liver function test showed a retention of dye, grade 1, and the liver had decreased in size to normal. The authors expected an uneventful recovery.

Physical and Toxicologic Properties of Carbon Tetrachloride—Carbon tetrachloride is a colorless, transparent fluid, derived from methane. It is similar to chloroform but is more toxic. It is volatile at room temperatures and is about 5 times as heavy as air. Its vola-

tility makes it accessible for inhalation and the fact that it is heavier than air makes proper ventilation a very difficult problem. The chemical is readily absorbed through the lungs, the skin and the gastrointestinal tract.

Poisoning from carbon tetrachloride of animals produces hemorrhage into the gastrointestinal tract and necrosis of the central portion of the liver lobule which can lead to acute yellow atrophy and cirrhosis. Sometimes diffuse nephritis results as a terminal development.

Workers engaged in the occupations of dry cleaning and shoe repairing, the manufacture and use of certain paints and in the vulcanizing rubber industry are those in which exposure to carbon tetrachloride fumes are most likely.

In the literature, there are many reports of acute poisoning from carbon tetrachloride, but comparatively few reports of hepatitis due to inhalation of the fumes of this chemical. Because of the rarity of the condition and possible industrial and medicolegal aspects of the problem, the authors considered the case a very important one.

In discussing the above case J. L. Bollman states that experimental work with animals indicates that the extent of hepatic damage due to administration of carbon tetrachloride can be greatly altered by variations in the diet of the animals. The resistance of the liver seems definitely greater when the diet is rich in carbohydrate. Animals seen in terminal stages of hepatic cirrhosis by long continued exposure to carbon tetrachloride appear to have recovered completely within a few months after discontinuation of the chemical if a diet rich in carbohydrates is given.

W. H. Graham¹¹ discusses 2 cases of acute poisoning with carbon tetrachloride in which the symptoms very closely simulated an acute abdominal condition

In discussing treatment the author states that in 1 case improvement was brought about in less than 12 hours by the intravenous injection of 10 cc. of a 10 per cent solution of calcium chloride.

DIGITALIS

Influence on Cardiac Pain—In order to determine whether digitalis has a direct constricting effect on the coronary arteries and, as a result of such action, increase the pain in patients suffering with attacks of angina pectoris, H. Gold, H. Otto, N. T. Kwit and H. Satchwell¹² studied and reported on 120 ambulant cardiac patients suffering with cardiac pain. The study was conducted during a period of 7 years. The duration of observation in any given case varied from 2 to 64 months, the average being 21 months.

The authors used as their criteria for the selection of these patients evidence of organic heart disease, absence of signs of congestion, cardiac pain on effort, doing little or no physical work and faithful co-operation.

The effect studied was the influence of digitalis on the severity and frequency of attacks of pain and on the capacity for effort without pain.

The results show variable departures from the regular status in about 50 per cent of the cases after digitalis was started. In approximately 15 per cent the pain was increased and in about 30 per cent it was diminished. Results very similar to the above were also obtained when a placebo was substituted for digitalis.

In most cases the change in pain failed to persist when administration of the drug was continued or failed to reappear during repeated courses of digitalis.

In the remaining cases in which the change recurred when the courses of digitalis was repeated, it was possible to digitalize fully without any apparent effect in pain by altering the form, color or flavor of the preparation of digitalis.

The authors conclude from these results that in cases of angina pectoris without congestion the possibility is negligible that the use of digitalis will, by direct action on the circulation, increase or diminish cardiac pain.

GENTIAN VIOLET

Therapeutic Value—R. L. Sutton, Jr.,¹³ discusses his experience with the use of gentian violet in the topical treatment of those external diseases wherein gram-positive bacteria play a part. The dye is a mixture of pentamethylpararosaniline chloride and hexamethylpararosaniline chloride, and is soluble in water, alcohol and chloroform and insoluble in petroleum fractions. The dye is nontoxic and nonirritative and can therefore be used with safety in the treatment of various forms of cutaneous disease such as seborrheic dermatitis, impetigo, eczema, paronychia, eczematoid ringworm, Vincent's angina, and ulcers of the leg. The substance has also been found superior to tannic acid in the treatment of burns, and as a preventive of autoinoculation in staphylococcal conditions of the skin.

Very good results are obtained by the author with the use of the dye in conjunction with superimposed wet dressings of either 1:5000 mercury bichloride, 1:500 aluminum acetate, or 1:3000 potassium bichloride. This method is particularly effectual in most secondarily infected dermatoses and in those primary dermatitides due to gram-positive organisms.

In the treatment of Vincent's angina all infected areas are swabbed with a 2 per cent solution of gentian violet, and the patient is then given a mouthwash of tepid water to prevent staining of the lips. Apart from the bacteriostatic action of the dye it also possesses well-marked granulating properties and is thus useful for the sterilization of closed cavities and the promotion of healing of open wounds.

In monilial pruritus of the inguinal or anal regions, and the accompanying disseminated eruptions, the daily application of 2 per cent aqueous solution of gentian violet and the superimposition of 1:3000 permanganate soaks will give quick relief.

The dye may be incorporated in a salve, but the author believes this to be a rather unsatisfactory method of use. The aqueous solution of 1 or 2 per cent for topical application and from 0.1 to 0.5 per cent for soaks or baths is the most practical way to use gentian violet.

GLYCERYL TRINITRATE

Unusual Reactions—Many patients suffering with hypertension experience rather severe reactions following the administration of glyceryl trinitrate. The nature and frequency of these reactions were studied by H. C. Lueth and T. G. Hanks.¹⁴

Fifty outpatient dispensary patients were selected who were suffering from hypertension or hypertensive heart disease. The patients were given, directly under the tongue, a chemically assayed solution of glyceryl trinitrate with a graduated pipette. The tests were made under standard basal conditions, with frequent blood pressure readings being made. Nine patients showed reactions, consisting of nausea, vomiting, syncope,

collapse, and involuntary passage of urine and feces.

These reactions in some cases followed doses as low as 0.24 mg ($\frac{1}{300}$ gram) and were more severe if the patient was sitting up than when he was lying down. Four tests to determine unusual vasomotor lability, *i e*, the Hines-Brown test, the histamine flare test, and changes in the pulse volume and observations of the capillaries of the skin were of no assistance in predicting these reactions.

GOLD

Gold Tribromide—*Therapeutics*—

J. Epstein¹⁵ reports on the use of gold tribromide in the treatment of 250 children suffering from pertussis. The results in this group in which gold tribromide was given as the only medication showed the duration of illness to be greatly shortened with an almost immediate improvement in the cough and in the general condition of the patients. In 100 children the cough had entirely subsided by the end of 3 weeks; in 75, by the end of 4 weeks; in 45, by the end of 4½ weeks; in 30, by the end of 5 weeks. The average duration of the illness in the 250 children treated with gold tribromide exclusively was 3½ weeks.

As a control, another 100 children suffering from pertussis were given the usual antiwhooping cough remedies, consisting of various drugs, vaccine and, to some, flavored water. The average duration of cough in this group was 10 weeks. Gold tribromide therapy in the hands of the author cut down the duration of the cough almost one-third and, also, has been of great help in relieving the violence and frequency of the coughing seizures.

Pharmaceutical Preparation—Dosage—Gold tribromide is an unstable and easily oxidized chemical and undergoes deterioration when dispensed in pills, capsules or aqueous solutions. It is therefore dispensed in a stable, assayed and palatable elixir known as elixir bromaurate. The average dose of the elixir for children is 1 teaspoonful every 4 hours, and 2 teaspoonfuls for adults.

Gold and Sodium Tetrabromide ($AuNaBr_4$)—Therapeutics—The author cites his limited experience with the use of gold and sodium tetrabromide in the treatment of epilepsy.

The drug was tried in 35 cases for a period of 6 months, and the results compared with those obtained by the use of various other commonly used drugs. The author concludes that the number of cases observed were too small and the time too limited for a full estimate of the therapeutic value of gold and sodium tetrabromide in the treatment of epilepsy. Nevertheless, after a fair trial, the author believes this new chemical will be shown to be superior to the present drug treatment.

Pharmaceutical Preparation—Dosage—Gold and sodium tetrabromide is available under the pharmaceutical name of Aurosodobrom.

The dosage for adults is 10 drops, for children 5 drops in water 3 or 4 times a day after meals.

HELIUM

U. H. EVERSOLE¹⁶ reports on the use of helium during either the induction or the maintenance of anesthesia in 110 cases.

Physical Properties Responsible for Clinical Uses of Helium—Helium is entirely inert, the basis for its clinical use depending entirely on its physical properties of low specific gravity and

rapid rate of diffusion. Helium is approximately one-eighth as heavy as oxygen and one-seventh as heavy as nitrogen, while a mixture of 79 per cent helium and 21 per cent oxygen is about one-third as heavy as air and slightly less than one-third as heavy as pure oxygen. Therefore, using the formula that F equals MA —when F is force, M is mass and A acceleration—the force required to move a given volume of 21 per cent oxygen and 79 per cent helium should be approximately one-third that required to move the same volume of air and slightly less than one-third that required to move the same volume of pure oxygen. The rate of flow of gases through narrow orifices is inversely proportional to the square root of their molecular weights. On this basis the rate of flow of a mixture of 79 per cent helium and 21 per cent oxygen through a narrow orifice should be about twice that of air. Because of these physical properties the addition of helium to any gas or mixture of gases will result in a lighter and more diffusible mixture which will require less muscular effort (force) to be moved.

Indications and Clinical Uses of Helium—The author states from his experience at the Lahey Clinic that the indications for the use of helium are comparatively few. This is evidenced by the fact that it has been attached to the gas machine for more than 2 years and has been used in relatively a small number of cases. During anesthesia, helium has been administered to patients in whom certain respiratory difficulties occurred, these difficulties resulting from stridor, respiratory obstruction or muscular weakness caused by spinal anesthesia. The author does not attempt to substitute the use of helium for unobstructed breathing, but in certain emergencies it has been of distinct value in holding the

patient until a tube could be inserted within the trachea.

In a second group of cases helium was used to facilitate breathing where a definite mechanical obstruction to respiration was present. These cases include postoperative hemorrhage into the tissues of the neck causing tracheal compression, or postoperative tracheal edema, as well as laryngospasm. Thirteen of the above cases were the result of hemorrhage or edema causing tracheal compression following thyroidectomy. In these patients obstruction and edema were present and in some cyanosis was marked when the patients were brought to the operating room. Here helium was administered only during the induction period, prior to the insertion of an intratracheal tube. The results show 53.9 per cent obtained complete relief, 30.7 per cent partial relief, while 15.4 per cent received no benefit.

In the second group of cases with mechanical obstruction, excluding the 13 mentioned above, helium was not added until the ordinary methods for relief of obstruction, such as extension of the chin, insertion of oral and nasal breathing tubes and pressure on the breathing bag, had been tried. In this group the results showed that in those patients with stridor alone, 61.5 per cent obtained complete relief, 33.3 per cent partial relief, and 5.1 per cent no relief. The patients with both stridor and obstruction showed 46.9 per cent obtaining complete relief, 36.4 per cent partial relief, and 16.7 per cent no relief.

Technic of Administration—1. Obstruction Present Before Anesthesia Is Established—A flow of approximately 3 liters of helium and 1 liter of oxygen is started and the mask is placed on the patient's face. The patient breathes this mixture for 5 to 10 minutes or until the obstruction is relieved,

the bag being emptied each time it becomes distended. The flow of helium is then stopped, oxygen decreased to the required amount for the patient and cyclopropane is added, usually at the rate of from 300 to 500 cc. per minute, until the patient is anesthetized.

2. When Obstruction Develops After Anesthesia Is Established—

The bag is completely emptied, and a flow of 1200 cc. of helium, 500 cc. of oxygen and 300 cc. of cyclopropane is started. It is usually necessary to maintain this rate of flow for from 5 to 10 minutes, emptying the bag each time it becomes distended, and watching the patient closely for the slightest degree of anoxemia. At the end of this time, the administration of the helium and the cyclopropane may be discontinued and the flow of oxygen continued at the rate of from 200 to 400 cc. a minute. Helium and cyclopropane are now added, at a rate just sufficient to compensate for any leaks that may be present in the system. In severe cases of obstruction moderate pressure on the bag is an additional help.

HEPARIN

Therapeutics—G. D. W. Murray and C. H. Best¹⁷ recount their experiences with the use of heparin as an anti-coagulant. In a series of 315 cases treated postoperatively with heparin injections not one case of phlebitis, thrombosis, or pulmonary embolism occurred. Seven cases of pulmonary embolism with infarcts arising from thrombophlebitis were also treated and there was rapid clinical improvement within 24 hours. With the use of injected heparin to keep the vessels clear, embolectomy was carried out successfully in 4 cases of embolism.

Administration—The method of administration was by intravenous drip, the injection being given in a superficial vein through an ordinary needle which was left in the vein continually for from 3 to 8 days.

Heparin was added to normal saline solution in an amount sufficient to cause the clotting time to be increased to approximately 15 minutes. Ten units of heparin to 1 cc. of saline was the usual proportion used, the solution being injected at a rate of approximately 25 to 30 drops per minute.

The injections were continued until the state of shock had passed and the blood pressure and circulation had returned to normal.

No toxic effects were noted, and only 4 patients developed postoperative hematomas; the hemorrhage stopped, however, when the heparin was discontinued, and all patients recovered. The authors caution that the drug should not be used when active hemorrhage is present, and the institution of heparin therapy should usually be started not sooner than 4 to 24 hours after operation.

In the selection of cases a blood study is necessary to determine the blood count, blood clotting time, bleeding time, prothrombin index and platelet count.

N. Holman and K. G. Ploman¹⁸ describe a case of thrombosis of the central retinal vein and one of the thrombosis of the posterior inferior cerebellar artery successfully treated with heparin.

IODINE

Indications in Hyperthyroidism—G. Crile, Jr.,¹⁹ discusses the indications for the use of iodine in the treatment of hyperthyroidism. The judicious use of iodine as a prophylactic measure has been most satisfactory in reducing the inci-

dence of endemic goiter in areas where it is prevalent. However, in regard to the use of iodine in treatment of established goiter, the drug is frequently employed in cases where it is clearly contraindicated. The author summarizes the indications for the use of iodine in hyperthyroidism as follows:

1. In patients with diffuse or nodular goiter in preparation for operation
2. In patients with mild recurrent hyperthyroidism associated with small goiters
3. After operation until the peak of the thyroid reaction is over
4. In small doses for a period of months after operation in patient with hyperplastic glands
5. Between the stages of divided operations
6. As a "therapeutic test" to aid in diagnosis

MANDELIC ACID

Therapeutics—The continued use of mandelic acid in the control of urinary infections has proved so effective that it is now an established therapeutic agent.

A general summary of the more recent advances in treating urinary infections with mandelic acid is discussed by W. Sheldon.²⁰ The introduction of ammonium mandelate during the past year has greatly facilitated treatment by making it unnecessary to prescribe a urine-acidifying salt, such as ammonium chloride, to maintain the pH of the urine below 5.5. In the majority of cases, ammonium mandelate alone will render the urine sufficiently acid, if the total amount of fluid ingested in 24 hours is kept at 1200 cc. or less. However, the necessity of testing the acidity of the urine each day is stressed by the author. A few drops of methyl red are added to 5 cc. of a fresh specimen of urine, which causes the urine to be tinted pink if the required degree of acidity has been reached, otherwise the urine turns an orange or yellow color.

Mandelic acid finds its chief use in chronic *B. coli* infections of the urinary tract. The author emphasizes the fact that one should not be too enthusiastic over results obtained with the use of the acid in these chronic urinary infections. Even if a chronic infection quickly clears under mandelic acid treatment the possibility of some underlying deformity of the urinary tract resulting in urinary stasis should always be thought of. Where any deformity is suspected a thorough investigation of the urinary tract should be made to settle the question of deformity, because it is only by correcting these deformities that relapses and ultimately permanent kidney damage can be prevented.

Dosage—E. N. Cook²¹ states the dosage of the acid must be maintained at 12 Gm. daily, 3 Gm. being given every 4 hours. With the advent of the newer preparations of the drug, the original dose of the acid must be regulated according to the concentration of the solutions used. Most satisfactory results have been obtained by administering the drug in prescribed dosage for a period of 6 to 12 days. If the urine is not free of bacilli at the end of this period it is better to discontinue the drug for 10 to 14 days and then institute a second course of treatment. This prevents the possibility of the organism from building up a tolerance to the drug and also lessens the danger of renal irritation from the acid.

MERCURIAL DIURETICS

Effect on Clinical Course of Congestive Heart Failure—A study of the duration of life of patients with congestive heart failure who had received intravenous mercurial diuretics was studied and reported by L. E. Hines.²² This study was stimulated by the ob-

servation of occasional unfavorable reactions in some patients and an impression that the life expectancy of many patients was not prolonged by the use of mercurial diuretics even though edema was controlled. Also, it was observed by the author that at times patients with uremic manifestations died shortly after they had become edema free after prolonged mercurial diuresis.

For the study of life expectancy Hines selected a group of patients with hypertensive and arteriosclerotic heart disease from Cook County Hospital, who were treated during 1935. The duration of life after the onset of congestive failure of the group treated with intravenous mercurial diuretics is compared with that of a group of patients from the same hospital studied and reported by N. Flaxman.²³ The results of this study indicate that the use of mercurial diuretics for the rapid removal of edematous fluid certainly fails to prolong life in the majority of cases. The figures actually, although they certainly are not conclusive, suggest a decrease in the duration of life after the use of mercurial diuretics.

In the 60 cases receiving mercurial diuretics there were 21 deaths attributable to uremia, against 31 deaths from uremia in the series of 189 cases who did not receive mercurial diuretics, the occurrence of uremia being almost twice as great in those patients receiving mercurial diuretics.

The author is of the opinion that one cannot conclude from this small series that mercurial diuretics have the capacity *per se* to produce uremia. The results do point to the necessity of a critical study of the arteriosclerotic patient with congestive failure before powerfully acting diuretics are used.

The author, therefore, in view of the above findings submits a plan of study

of each patient with congestive failure before a mercurial diuretic is used. The plan is as follows:

1 Salyrgan is used only when rest, digitalis and xanthine diuretics fail to produce the desired diuretic response.

2 The preliminary examination includes estimates of the plasma chloride content, the urea nitrogen content, the carbon dioxide combining capacity and the blood phenol content, the drug is not given if markedly abnormal values are observed

3 During the period of diuresis, interval determinations are made, frequently if symptoms suggest the onset of uremia

4 Marked lowering of the plasma chloride content if associated with mental symptoms points to a need for intravenous administration of saline solution

5 Lowering of the carbon dioxide combining capacity with symptoms of acidosis requires restriction of ammonium chloride and administration of sodium bicarbonate and dextrose.

6 The first dose of salyrgan should be given intramuscularly to eliminate the danger of the rare hypersensitive reaction

7 Secretions of large amounts (from 5 to 10 liters daily) is more dangerous than secretion of smaller amounts, doses of from 0.25 to 0.5 cc in some cases produce an adequate response

Mercurial Suppositories As a Diuretic—Therapeutics—The use of mercurin suppositories on 20 occasions in 10 patients with varying degrees of cardiac decompensation is reported by J. Flexner²⁴. These patients had routinely been treated by bed rest, sedation, digitalis and restricted fluid intake. In 17 instances (85 per cent) a diuresis ranging from 1950 cc to 8750 cc in 24 hours resulted from the use of the suppositories. One of the failures responded with a diuretic effect after 3 days of ammonium chloride therapy. The treatment also failed in 1 other case on 2 occasions in which definite renal complications were present.

The author recommends the use of ammonium chloride as an adjunct to the

mercurial suppositories in order to obtain the maximum diuretic effect.

NICOTINIC ACID

D. T. Smith, J. M. Ruffin and S. G. Smith²⁵ report their experience with the use of nicotinic acid in the treatment of a very severe case of pellagra. The patient, a white male, 42 years of age, gave a history of having recurrent pellagra for a period covering 15 years.

The patient was fed a basic diet, deficient in the pellagra preventive factor, throughout his entire period of study. His condition became progressively worse and, by the end of the first week, he refused to eat, became completely disoriented and developed delusions of persecution.

Therapeutics—Treatment was limited to nicotinic acid (Eastman), the patient remaining on the basic diet. A solution was prepared in sterile physiologic solution of sodium chloride so that 1 cc contained 2 mg of nicotinic acid. On the seventh day after admission the patient was given intramuscularly 60 mg. of the drug. On the next day he received intravenously 60 mg dissolved in 1000 cc of 5 per cent dextrose in saline solution. For the next 6 days he received 60 mg daily, the intramuscular and intravenous routes being alternated. On 1 occasion he was given intramuscularly 60 mg dissolved in 6 cc of physiologic solution of sodium chloride. On 2 successive days 60 mg was dissolved in 100 cc of water and given orally. He was given, in all, 720 mg of nicotinic acid.

No reaction followed the use of the drug by the oral route. Marked flushing of the face, neck, chest and arms appeared a few minutes after intramuscular and intravenous injections and lasted for approximately 15 minutes.

The authors describe the results of the treatment as dramatic. The appetite improved markedly within 24 hours. The mental condition began to improve after 48 hours and he became entirely rational after 6 days of treatment. The skin of the face began to improve after 3 days of treatment, and was entirely normal after 12 days. On the seventh day of treatment the T-waves of the electrocardiogram returned to normal. The cremasteric and the abdominal reflexes were present after the 12th day.

The effectiveness of nicotinic acid in curing the lesions of the mucous membranes due to pellagra is substantiated by the report of T. D. Spies, C. Cooper and M. A. Blankenhorn²⁶. In the 17 cases treated by the authors, nicotinic acid cured the pellagrous glossitis, stomatitis, ptyalism, vaginitis, urethritis and proctitis very promptly. However, nicotinic acid had no apparent effect in 4 cases of nonpellagrous glossitis. Severe cases of moist ulcerating pellagrous dermatitis did not seem to be specifically benefited by nicotinic acid. However, the acute fiery red, erythematous lesions blanched within 24 to 48 hours after nicotinic acid was started. The patients with mental symptoms were too severely ill to remain on an unbalanced diet for a period long enough to determine definitely the effectiveness of nicotinic acid on this phase of the disease.

Dosage—According to the authors the maximal and minimal dosage of nicotinic acid for oral or parenteral use has not been determined, however, 0.5 Gm. daily, given in 5 doses of 100 mg. each, is safe and effective in the usual case of pellagra.

For parenteral injection 50 to 80 mg. a day, in sterile physiologic solution of sodium chloride, were effective when injected intravenously. Nicotinic acid was

found effective by the authors when used by hypodermoclysis; 100 mg. of the acid in 1 liter of physiologic solution of sodium chloride.

H. L. Schmidt and V. P. Sydenstricker²⁷ report on their results in the treatment of 33 known chronic pellagrins. Sixteen patients were treated with nicotinic acid given in doses of 100 mg. twice weekly; 17 were used as controls and given 90 Gm. of brewers' yeast daily. The patients were observed over a period of 6 weeks.

From the results the authors concluded that, in their hands, nicotinic acid in doses of 100 mg., twice a week, was not effective in preventing relapse in known chronic pellagrins.

Their experience indicates, however, that in the treatment of acutely ill patients, small daily doses may prove more effective, and even entirely satisfactory.

OXYGEN

The modern therapeutic efficacy of oxygen therapy in medicine originated during the World War when it was demonstrated to have a very definite beneficial effect on soldiers gassed with pulmonary irritants. Following the war considerable work has been done on the therapeutic use of oxygen in concentrations varying between 40 and 60 per cent. The recent development in commercial and military aviation has emphasized the dangers of anoxemia to which pilots and passengers are exposed when flying. In order to supply oxygen routinely to both pilots and passengers, W. M. Boothby, W. R. Lovelace and A. H. Bulbulian²⁸ report the development by them of an oxygen inhalation apparatus of a mask type with rebreathing bag, especially designed to meet the needs of aviation. In addition, the authors report that this

oxygen inhalation apparatus is applicable to the therapeutic administration of oxygen or of oxygen-helium mixtures. Also, not only can the ordinary inhalation of 50 to 60 per cent oxygen, such as is now generally accomplished in oxygen tents, be effected at about a fifth of the usual cost to the patient, but that, in addition, higher concentrations of oxygen can be equally conveniently administered even up to concentrations of 100 per cent oxygen if desired.

The ability to administer oxygen in these higher concentrations makes possible a new field of investigation regarding the increased value of high concentrations of oxygen, not only in the conditions for which oxygen is customarily given, but also for many new conditions for which oxygen therapy has not yet been tried. The authors state that concentrations of oxygen varying from 90 to 100 per cent have been administered to approximately 100 patients for periods of 1 to 4 days, with intermissions of a few minutes every 3 to 4 hours, without any evidence of pulmonary irritation. The authors advise against longer periods of administration at the present, and as soon as the patient improves, the concentration of the gas should be reduced.

Physiologic Principles Underlying Administration of 100 Per Cent Oxygen—W. M. Boothby²⁹ cites 4 physiologic principles or factors on which the value of approximately 100 per cent concentration of oxygen in the inspired air is based.

1 Inhalation of approximately 100 per cent concentration of oxygen increases the amount of oxygen carried by 100 cc. of blood from 20 cc. to between 22 and 23 cc., an increase of 10 to 15 per cent. This is accomplished as follows: oxygen is present in the blood in 2 states: (a) A small amount in simple solution according to Henry's law of solution of gases

in liquids, and (b) a much larger amount in chemical combination with hemoglobin.

2 Under normal conditions, as the blood passes through the capillaries, the rate of circulation is so regulated that it gives up about a third of its oxygen content and enters the veins about 60 per cent saturated. The partial pressure of oxygen in the capillaries at this degree of saturation will be approximately 35 mm. of mercury. If for any reason the rate of circulation is decreased, the blood may give up nearly 80 per cent of its oxygen as it passes through the capillaries; therefore, the venous blood is only 20 per cent saturated and exerts a partial pressure of oxygen of only 14 mm. instead of a normal pressure of 35 mm. If pure oxygen is inhaled, it results in an increase of percentage saturation of the hemoglobin of the venous blood to about 33 per cent and the corresponding partial pressure of oxygen will be increased from 14 to 21 mm. This results in a 50 per cent increase in the oxygen tension in the capillaries, which produce an even greater percentage increase in the oxygen tension of the tissues.

3 The inhalation of pure oxygen has been used by the authors to relieve abdominal distention. The gas causing abdominal distention is nearly 70 per cent nitrogen. By using pure oxygen inhalation, the nitrogen in the blood is quickly washed out in the lungs and the blood will have a much greater capacity for picking up nitrogen when it passes through the capillaries of the intestinal wall, and then again be given off when it reaches the lungs. By the use of pure oxygen inhalations the authors are able to reduce marked abdominal distention in 18 to 24 hours. The headache following encephalography either will be greatly reduced or will cease entirely in from 2 to 4 hours after administration of oxygen is begun. Here the rapid removal of the nitrogen from the sub-arachnoid space and the ventricles and also, the decrease in the intensity of the cerebral tissue anoxemia caused by the closing of some capillaries are the 2 factors which play a role. Subcutaneous emphysema, especially that which accompanies gas gangrene, can be rapidly decreased by the administration of oxygen in high concentrations.

4 Another factor which plays an important part in certain cases is a bactericidal effect of high oxygen concentrations on certain bacteria. This action is very striking in cases of gas gangrene and tetanus, which are caused by organisms which are definitely anaerobic.

During the past 5 months at the Mayo Clinic 125 patients have been given oxygen or oxygen and helium therapy by means of the inhalation apparatus devised by Boothby, Lovelace and Bulbulian. The authors have not studied a large series by cases of any 1 type, but attempts are being made to gauge its possibilities in a number of conditions. At present, cases of congestive heart failure, postoperative pneumonia, asthma, gaseous distention and severe headaches following encephalography have been treated with concentrated oxygen or oxygen and helium with definite success.

The authors conclude that the ability to administer high concentrations of oxygen economically opens up an entirely new field of oxygen therapy; many types of conditions hitherto not materially helped by the ordinary concentrations of oxygen, available in oxygen tents, have been definitely benefited by high concentrations of oxygen.

PARALDEHYDE

Idiosyncrasy—J. Kotz, G. B. Roth and W. A. Ryon²⁹ report on a case of a 31-year-old patient in which coma and death occurred after 31 cc of paraldehyde was given by rectum as a single dose in the beginning of labor. Death in this case according to the authors, was the result of unusual susceptibility to paraldehyde. The hypersusceptibility was regarded as being probably produced by pre-existing toxic hepatitis not discovered until necropsy.

Toxicology of Paraldehyde—The authors summarize their extensive review of the literature concerning the toxicologic aspects of paraldehyde in order to show that the dose used in their fatal case was not excessive under ordinary conditions. Also, toxicologists, pharmacologists and clinicians who have used

the drug for sedation other than as a soporific consider paraldehyde to be a relatively nontoxic substance.

The authors since January, 1935, have used paraldehyde in more than 600 labor cases with very gratifying results. They conclude that it is an effective analgesic which is relatively quite safe, and its use should not be discontinued because of their 1 fatality incident to its administration. However they do believe that the use of the drug should be confined to hospital patients only, since the patients under its influence require special care during labor.

PERCOMORPH LIVER OIL

Therapeutics—Percomorph oil is natural fish oil having a vitamin D and vitamin A concentration of approximately 100 times that of cod liver oil (U. S. P. XI).

The antirachitic properties of this oil were tested out by R. L. Roddy, E. K. Rose, P. J. Hodes and J. C. Gittings³⁰ in a series of 100 infants under 6 months of age who were being artificially fed, and were free from any apparent disease. Children showing signs of rickets were not excluded from the series. The oil used in this study contained 8500 units of vitamin D and 60,000 units of vitamin A per Gm.

The initial dosage used at the beginning of the test was 10 drops of oil per day, but later this amount was reduced to 5 drops, being gradually increased up to 10 or 10.5 drops per day. Careful x-ray examination of the upper and lower extremities was made at the beginning and the end of the test. In 16 infants the initial x-ray examination showed definite signs of rickets, but the final x-ray showed all osseous changes had completely healed. Of the remaining 84 infants 75 per cent were entirely

protected from the development of rickets over a test period of $4\frac{1}{2}$ months, and this group included 11 premature babies

PICROTOXIN

Therapeutics—The beneficial effect of the use of picrotoxin as an antidote in cases of poisoning due to the barbiturates is reported on by W. J. Bleckwenn and M. G. Masten³¹

The authors discuss the use of picrotoxin in 6 patients with barbiturate poisoning from self-administered drugs used with suicidal intent. Five of the 6 cases recovered completely from the effect of the poison. One case, however, failed to recover after having received a total of 669 mg. of picrotoxin. In spite of this exceedingly large dose of picrotoxin there was no evidence of toxic or depressing effects attributable to the drug. Failure to recover in this case was attributed to cerebral anoxia and edema and finally medullary death.

Dosage and Method of Administration—The authors recommend that picrotoxin be administered intravenously in a 1:1000 solution at the rate of 1 cc. per minute. Picrotoxin should be administered early while other emergency treatment such as gastric lavage and oxygen administration are being carried out. The first notable effect of picrotoxin will be an increase in the depth of respiration and a rise in the blood pressure. Slowing of the pulse rate and an improvement in its quality are frequently noted. The return of the pupillary and corneal reflexes, or twitching if the return of the reflexes is missed is the signal that the convulsive stage is approaching, and the administration of the drug stopped. Patients suffering from the effects of a short acting barbiturate usually regain consciousness promptly, while others may pass from a deep plane of anesthesia

to a lighter one. These latter patients although still unconscious are considered in a safe stage, failure to regain consciousness promptly probably being due to cerebral edema from which recovery may be hastened by diuresis. Other supportive measures emphasized by the authors as necessary for effective treatment of barbiturate poisoning are: (a) Gastric lavage and purgation; (b) continuous oxygen; (c) diuresis by parenteral fluids and intravenous sucrose, and (d) the administration of dextrose to prevent acidosis.

E. A. Rovenstine³² discusses the use of intravenous infusion of picrotoxin in 4 cases of severe barbiturate poisoning with coma. Complete recovery was obtained in 3 cases, but the fourth case, a man of 57, who had taken 500 grams of veronal in an attempt at suicide, made temporary recoveries under the influence of picrotoxin but finally died on the eighth day of his illness. In the first case reported the picrotoxin was given in 3 mg. doses by the intravenous route until 129 mg. had been administered at irregular intervals. In the second case 48 mg. was given during an hour, this stimulated respiration, but was followed by twitching of the mouth and vomiting. In the third case the patient was in deep coma, the result of having taken 75 grams of sodium luminal. Picrotoxin was administered intravenously, 1 mg. per minute up to 15 mg. when the patient came out of coma. A relapse occurred 4 hours later and infusion was restarted, 1 mg. picrotoxin being given per minute up to 30 mg., followed by gastric lavage, 1 grain calomel in 10 cc. water being left in the stomach. Mercupurin (1 cc.) was given intramuscularly and 8 mg. picrotoxin, this was followed by muscular twitching. Doses of 3 mg. picrotoxin were given every 10 to 30

minutes intramuscularly—in all the patient received 122 mg. of the drug.

PURINE DERIVATIVES

Comparative Therapeutic Value in Angina Pectoris—M. G. Brown and J. E. F. Riseman³³ investigated 17 patients suffering from coronary arteriosclerosis in order to determine the comparative efficacy of caffeine, theobromine and theophylline derivatives in the treatment of angina pectoris. The usual clinical methods plus the amount of work under standard conditions which patients could perform before heart pain developed were used to determine the therapeutic efficacy of each of the preparations used.

Preparations Used and Dosage, Results—Each preparation was given 4 times daily; on arising, after lunch, after supper and on retiring.

1. Theophylline Derivatives—Six theophylline preparations were used: 2 were relatively insoluble—theophylline, 3 grains (0.2 Gm.) and theophylline with calcium salicylate, 8 grains (0.5 Gm.), the remaining 4 were more soluble—theophylline with sodium acetate $2\frac{1}{2}$ grains (0.15 Gm.), theophylline with ethylenediamine 3 grains (0.2 Gm.), theophylline with methylglucamine $2\frac{1}{3}$ grains (0.14 Gm.), and theophylline mono-ethanolamine 3 grains (0.2 Gm.).

The most effective preparation was theophylline with sodium acetate. Eighty per cent of the patients treated with theophylline with sodium acetate were benefited, with 27 per cent showing 50 to 100 per cent increase in exercise tolerance. The second best theophylline preparation was theophylline with calcium, which showed 67 per cent of the total number treated being benefited, with 13 per cent having a 50 to 100 per cent increase in exercise tolerance.

2. Theobromine Preparations—Theobromine with sodium acetate in doses of $7\frac{1}{2}$ grains (0.5 Gm.) 4 times a day was far superior to all other preparations of theobromine and was equally as effective as the best of the theophylline compounds. Seventy-seven per cent of the total number of patients treated were benefited by theobromine with sodium acetate, with 24 per cent having a 50 to 100 per cent increase in exercise tolerance. Theobromine with calcium salicylate (15 grains—1 Gm.) was also of considerable value and about equal to theophylline with ethylenediamine or theophylline. Theobromine, 5 grains (0.3 Gm.), and theobromine with sodium salicylate $7\frac{1}{2}$ grains (0.5 Gm.) were about equal in their benefits and were definitely less effective than other preparations.

Caffeine Derivatives—Caffeine citrate was the only preparation used. From results obtained by the authors, the drug is apparently of little value in angina pectoris, only 1 patient in the series showing questionable benefit from its use.

Combinations of Sedative with Purines—Two preparations, theobromine with phenobarbital and theophylline mono-ethanolamine with amytal, were used. The increase in tolerance for work was approximately the same as after the use of the purine derivative without the sedative. The only practical advantage from the use of sedatives in the treatment of angina pectoris is that it makes the pain easier to bear.

SNAKE VENOM

Therapeutics—W. F. Swett³⁴ reports on the use of moccasin venom in 6 cases in the control of postoperative ocular hemorrhage.

In the first case, hemorrhage occurred the first day following operation and con-

tinued to ooze in spite of all treatment for 10 days. Moccasin venom stopped the oozing immediately after the first injection of 0.4 cc. As soon as the bleeding had stopped the blood disappeared from the anterior chamber, allowing the wound to be closed completely 4 days later. The same results were obtained in 4 similar cases. The author's experience deals only with those cases showing a tendency to bleed after operation and he has found that 0.5 cc. given daily for 1 week has been sufficient to control the hemorrhage. He believes that the ideal method in which to use snake venom would be to give the injections before operation to prevent the complications from arising if possible.

Cobra Venom—D. I. Macht³⁵ reports on the use of cobra venom for its analgesic effect in cases of intractable pain. The drug in sufficiently small doses has been found by the author to be an efficient therapeutic agent for the relief of pain, particularly that of advanced malignant disease. The author has also extended its use to the treatment of certain chronic nonmalignant diseases accompanied by severe pain. Its action, like morphine, depresses pain areas in the cerebrum but it differs from morphine in that its analgesia is slower in onset and longer in duration.

Very favorable results are reported by the author in treating the severe pains in such conditions as *tic douloureux*, chronic arthritis and cases of angina pectoris with subacute, long-lasting paroxysms of pain.

A relatively new indication for the use of cobra venom cited by the author is its administration to patients afflicted with advanced Parkinson's disease. At the time of publication 15 cases had been studied and the author reports that in about 50 per cent the pain and spasticity have been definitely relieved.

Dosage — The usual dose of cobra venom recommended by the writer is 5 mouse units. A mouse unit being the quantity of cobra venom solution required to kill a white mouse weighing 22 Gm. within 18 hours after its intraperitoneal injection with the drug. The usual procedure is to inject $2\frac{1}{2}$ mouse units the first day, and on the following day 1 cc. (5 mouse units) is injected. Five mouse units each are injected for several successive days until a definite analgesia is noted or a contraindication for the use of the drug is encountered. Once analgesia is established, patients may usually be kept comfortable with 2 or 3 injections of 5 mouse units each week. The injections are given intramuscularly. The author states that up to the present time no signs of addiction in the narcotic sense of the word have been noted after as much as a year's treatment with cobra venom.

SODIUM CHLORIDE

Therapeutics—H. R. Sandstead and A. J. Beams³⁶ studied the effect of the oral administration of from 15 to 90 Gm. daily of sodium chloride on 13 diabetic patients complaining of pain who had not been relieved by the usual diabetic management. The pain was of neuritic origin in 10 and of arteriosclerotic origin in 3. All the patients obtained complete or marked relief of the neurotic symptoms after the administration of sodium chloride. The relief of pain was accompanied by signs of improvement in the vascular disease in the patients with arteriosclerotic pain and by improvement in the circulation of those with neuritic pain, as shown by the histamine test.

From the observations made it appears that ischemia due to the accompanying vascular disease is responsible for the neuritic symptoms. The authors

conclude that sodium chloride appears to be the rational treatment for the neurocirculatory complications of diabetes.

SODIUM DIPHENYL HYDANTOINATE

Following the successful experimental use of sodium diphenyl hydantoinate in protecting animals from electrical induced convulsive seizures, H. H. Merritt and T. J. Putnam³⁷ studied and reported their experience with the use of the drug in patients suffering from repeated convulsive seizures.

Chemistry—Sodium diphenyl hydantoinate is a derivative of glycolyl urea and is somewhat similar structurally to the barbiturates. It is a colorless white powder with a bitter taste, it is soluble in water, slightly soluble in alcohol and insoluble in benzene and ether. The aqueous solution shows a pH of 11.7.

Therapeutics—In the 118 patients with frequent grand mal attacks the use of sodium diphenyl hydantoinate resulted in complete relief of the attacks in 68 (58 per cent) and a marked reduction in the number of attacks in an additional 32 (27 per cent). In 18 (15 per cent) there was little or no improvement over the previous condition with bromides or phenobarbital therapy.

In 74 patients with frequent attacks of petit mal, complete relief was obtained in 26 (35 per cent) and in 36 (49 per cent) there was a marked reduction in the number of attacks.

In 12 (16 per cent) there was no improvement noticed over previous forms of therapy.

Of the 6 patients with psychomotor equivalent attacks there has been complete relief in 4 (67 per cent) and a very marked reduction in the frequency of attacks in 2 (33 per cent).

Dosage—For an adult the dose varied between 0.2 and 0.6 Gm. a day depending on therapeutic effect and toxic reactions. Generally adult patients were given a dose of 0.1 Gm. 3 times a day, and increased to a maximum of 0.2 Gm. 3 times a day if therapeutic effects were not obtained.

Small children were started on 0.1 Gm. twice daily, increased up to 0.4 or 0.5 Gm. daily until the optimum therapeutic dose was determined. Gastric symptoms were avoided in some by giving the drug along with or following the meal rather than before it.

Toxic Reactions—1. Minor toxic symptoms, such as dizziness, ataxia, tremors, blurring of vision, diplopia and slight nausea were encountered in 15 per cent of the cases treated. Toxic symptoms of this type usually occurred between the third and tenth day of treatment, and were relieved by reducing the dosage. Dosage could usually be increased after a few days if convulsive seizures were not controlled on the reduced dosage.

2. More serious toxic reactions consisting of dermatitis and purpura were encountered during the use of sodium diphenyl hydantoinate. Dermatitis occurred in 10 cases, and in 1 was considered serious. The skin reactions were of erythematous scarlatiniform or morbilliform nature and the rash disappeared in all patients except 1 regardless of whether the treatment was discontinued. Purpuric lesions developed on the buttock in 1 case approximately 2 months after treatment was started. Blood studies were negative, however, and it was not necessary to interrupt treatment.

Contraindications—The authors at present feel that sodium diphenyl hydantoinate should not be given to elderly persons with hypertension or any evi-

dence of cardiorenal disease, or to debilitated patients.

Conclusions—The authors believe sodium diphenyl hydantoinate is a very valuable drug in the treatment of epilepsy, but, for the present, should be restricted to those patients who do not respond to the less toxic forms of therapy previously used

SULFANILAMIDE AND RELATED COMPOUNDS

The passage of time, coupled with accumulated data on experimental studies and clinical observations, enables one to confirm early impressions on the therapeutic efficacy of sulfanilamide in certain types of infections. The field of therapeutic usefulness for the compound has steadily increased, but not without a more thorough knowledge of its limitations and dangers.

Therapeutic Indications—A review of the clinical experiences relative to therapeutic effectiveness and toxic manifestations of sulfanilamide and related compounds is reported on by E. G. Bannick, A. E. Brown and F. P. Foster.³⁸ The therapeutic efficacy of sulfanilamide in the treatment of infections due to hemolytic streptococci, meningococci, gonococci and in infections of the urinary tract caused by organisms other than the streptococcus faecalis seem well established in the minds of the authors.

The results thus far with the use of sulfanilamide in the treatment of infections due to the pneumococcus are inconclusive, and specific serum should still be the method of choice in these infections. From the results of experimental work, the combination of specific serum and sulfanilamide may be indicated in certain selected cases, and the use of sulfanilamide alone in cases of pneumonia

of long duration, or in the absence of specific serum.

Results thus far have been uniformly poor in treating infections due to staphylococcus aureus, staphylococcus albus and streptococcus viridans with sulfanilamide.

The authors have experienced varying results in the treatment of undulant fever with sulfanilamide, and in 1 case of tularemia no benefit was noted from the use of the drug.

The results have been generally unsatisfactory in the treatment of rheumatic fever, which is in accord with the observations of H. F. Swift, J. K. Moen and G. K. Hirst.³⁹

Dosage—The subject of optimal dosage of sulfanilamide is still unsettled in the minds of Bannick and his coworkers. However, they believe dosage depends chiefly on the type and severity of the infection, and that in fulminant cases 10 mg. of the drug per 100 cc. of blood seems to be a satisfactory concentration. In milder cases, concentrations of 5 to 7 mg. per 100 cc. of blood will frequently suffice, and can usually be realized with daily doses of 4 to 5 Gm. In general, the authors seem to favor relatively large doses of the drug, with uniform intervals between doses for the production of best results. However, the results of the experimental work conducted by E. E. Osgood,⁴⁰ using cultures of human bone marrow, would seem to indicate that much smaller doses than are ordinarily used should be therapeutically effective. They recommend the effective concentration of sulfanilamide as 1:100,000, only about one-tenth of that now ordinarily maintained in the blood stream. However, the authors believe that this experimental observation requires considerably more clinical confirmation before it is justifiable to employ smaller doses in seriously ill patients.

Toxic Manifestations—Bannick, *et al*,³⁸ believe that sensitivity and idiosyncrasy explain most of the toxic manifestations encountered during treatment with sulfanilamide. Manifestations due to idiosyncrasy are rare and usually serious, while those due to sensitivity are more common and usually mild, unless ignored. The authors emphasize the point that mild toxic symptoms such as cyanosis, abdominal cramps, diarrhea, cutaneous lesions, fever and paresthesias should not be treated too lightly or ignored. Persistence of mild toxic symptoms following a rest period from medication or in spite of reduction of dosage of the drug is sufficient indication to discontinue its use permanently. The general opinion at present is that the most serious toxic effects that have been observed from the use of sulfanilamide are those upon the peripheral blood and the hemopoietic system.

Sulfanilamide Derivatives (Di-Methyl-Di-Sulfanilamide)

Therapeutic Efficacy and Toxicity Bannick and his coworkers cite their experience with the use of di-methyl-di-sulfanilamide in the treatment of approximately 70 patients at the Mayo Clinic from September to December, 1937. In the group treated with di-methyl-di-sulfanilamide it was found that its therapeutic effectiveness was approximately the same as that of sulfanilamide. However, of striking interest was the rarity and mildness of toxic symptoms attributable to the new compound. Only 5 cases of the entire group treated showed mild toxic symptoms of malaise, mild nausea, fever, dermatitis and mild vertigo. It is also interesting to note that 7 cases were able to tolerate di-methyl-di-sulfanilamide in therapeutic doses after sulfanilamide had been tried several times and finally had to be dis-

continued permanently due to recurring toxic manifestations to the drug. No changes in the blood count or carbon dioxide combining power of the blood plasma attributable to the use of di-methyl-di-sulfanilamide were noted in their group of patients.

In 2 cases treated with di-methyl-di-sulfanilamide a very troublesome, and unusual complication of peripheral neuritis occurred. Both patients were taking large doses of the drug for a period greater than 14 days.

The authors conclude that, although di-methyl-di-sulfanilamide, in general, appears to be less toxic than sulfanilamide, its clinical application for the present time has been greatly reduced due to the possible occurrence of peripheral neuritis following its use.

Neoprontosil (Prontosil Soluble) Therapeutics and Toxicity—Another group of 93 patients studied and reported on by Bannick and his coworkers were treated with neoprontosil either alone or in conjunction with other sulfanilamide drugs. The drug was administered orally in 5-grain tablets or capsules in doses approximately the same as for sulfanilamide. The drug is quickly absorbed from the gastrointestinal tract and rapidly appears in the blood and urine. The therapeutic indications for the use of neoprontosil are essentially the same as for sulfanilamide.

Also, the therapeutic effectiveness was found to be about equal for the 2 compounds, but the incidence and severity of toxic reactions were much less following the use of neoprontosil than they were following treatment with sulfanilamide. W. E. Herrell, and A. E. Brown⁴¹ present their further impressions of the value of neoprontosil (oral). They conclude that neoprontosil possesses therapeutic properties similar to those of sulfanilamide, although, at times, its

therapeutic effectiveness may be slightly less than that resulting from sulfanilamide

Oral administration is the method of choice in administering the drug. The toxicity of neoprontosil seems to be definitely less than that of sulfanilamide

2. (p-Aminobenzenesulphonamido) Pyridine M. & B. 693—*Experimental Studies*—A considerable number of reports have appeared in the British medical literature during the past few months concerning the use of a new sulfanilamide derivative, M. & B. 693 (2 (p-Aminobenzenesulphonamido) pyridine), in the treatment of pneumonia

Experimental work carried out by L. E. H. Whitby,⁴² showed that the action of M. & B. 693 was similar to that of sulfanilamide in hemolytic streptococcus and meningococcus infections in mice. It was also found to have a definite action on pneumococcus Types I, VII and VIII, and, to a lesser extent, on Types II, III and V. The drug, according to the observations of Whitby, caused degeneration and finally disappearance of the capsule of the pneumococcus. In animals, the reports indicate M. & B. 693 has a low toxicity and is active in relatively small doses

Clinical Use—G. M. Evans and W. F. Gaisford,⁴³ reported on the use of M. & B. 693 in the treatment of 100 cases of pneumonia, using as a control group 100 cases which received various other forms of therapy. The mortality rate in the group treated with M. & B. 693 was 8 per cent, as compared with a 27 per cent mortality in the control group. The authors note that of the 8 fatal cases in the treated group, 6 cases received less than the minimal adequate dosage

H. F. Flippin and D. S. Pepper,⁴⁴ give a preliminary report on the use of M. & B. 693 in the treatment of 4 cases of pneumonia. In 1 case, both the drug and type specific serum were used. All

4 cases recovered. The experimental studies and clinical reports thus far suggest that this drug does have a definite effect upon the pneumococcus, and that extended use of the drug is indicated to properly evaluate its therapeutic effectiveness

A more recent report concerning the therapeutic efficacy of M. & B. 693 in the treatment of lobar pneumonia is given by S. C. Dyke and G. C. K. Reid.⁴⁵ Eight cases of lobar pneumonia comprise the above series, and treatment with M. & B. 693 was commenced from 12 hours to 4 days after the onset of the illness. Blood cultures were taken from 3 of the patients in the series, but all failed to give any growth. In order not to complicate the investigation, no serum was given to any case, and all other forms of treatment, other than symptomatic, were withheld

In every case the clinical improvement following the administration of the drug was prompt and striking. Within 12 to 24 hours the temperature and pulse fell by crisis, and there was a decided improvement in the clinical condition of the patients. The authors recognize the fact that the course of lobar pneumonia varies greatly from case to case, and that early crisis may occur. However, the consistent and uniform response to the administration of M. & B. 693 in all cases seems to indicate that the drug was definitely effective in controlling the infection

V. E. Lloyd, D. Erskine and A. G. Johnson,⁴⁶ report their results with the use of M. & B. 693 in the treatment of gonorrhea. The series consists of 108 consecutive male outpatients with a urethral discharge of not more than 1 week's duration in which gonococci were demonstrated before the start of treatment

Oral medication was used alone in 84 cases, and oral medication plus injections

in 24 cases. Twenty-eight cases failed to carry out the treatment, or defaulted. Of the remaining 80 cases, in 68 (85 per cent), treatment was considered successful according to the author's standards, while 12 cases (15 per cent) were unsuccessful.

From the above results the authors conclude that M. & B. 693 is markedly superior to sulfanilamide, or other sulfonamides in their hands in treating gonorrhea.

Also, the authors point out another definite advantage of M. & B. 693, namely, that when this new compound is used there is no need for delay in the commencement of treatment, as was the case with sulfanilamide. This, of course, reduces the risk of complications and the danger of infection to others.

Further evidence of the value of M. & B. 693 in the treatment of acute gonorrhea is reported by E. E. Prebble.⁴⁷ Approximately 100 cases of acute gonorrhea were selected for study, in each the gonococcus was demonstrated in the purulent discharge from the urethra.

The results of their study showed that the highest proportion of successes was in those cases treated by chemotherapy plus irrigations. The author also notes the important fact that it does not seem necessary to delay treatment with M. & B. 693 for more than 8 days as has been shown to be advisable with sulfanilamide.

Dosage and Administration—In patients suffering from lobar pneumonia, Evans and Gaisford administered M. & B. 693 orally, usually with an initial dose of 2 Gm., followed by 1 Gm. every 4 hours. This dose was maintained until a total of 25 Gm. of the drug had been given. In some of their cases a total of 9 Gm. was given during the first 24 hours. Dyke and Reid recommend a dose of 4 tablets (2 Gm.) followed by 2

tablets (1 Gm.) every 4 hours for 20 hours and, thereafter, 2 tablets every 6 hours. Administration of the drug should last at least 5 days, no matter how favorable the clinical condition of the patient might be. This gives a total dosage in 5 days of approximately 56 tablets (28 Gm.). The authors stress the fact that the drug should not be discontinued on the first appearance of a favorable change in the patient's condition. This was done in 2 cases studied by the authors, and relapses resulted, which, however, responded to the re-administration of the drug.

As a rule, children tolerate the drug well, and while the dosage must be reduced it need not be in proportion to body weight. The authors cite a case of a child just over 1 year of age suffering from a meningococcal infection who was given 1 tablet of M. & B. 693 every 4 hours (3 Gm. in 24 hours) with no bad effect.

In regard to cases suffering from gonorrhea, Lloyd and Erskine followed the following plan of dosages. Those patients receiving oral medication were given 3.0 Gm. of M. & B. 693 daily for a period of 2 weeks and then 1.5 Gm. daily for an additional week.

In the more recent cases it was proven possible to reduce the dosage, so that now 3.0 Gm. are administered daily for 5 days followed by 1.5 Gm. for 5 days.

Recently M. & B. 693 has become available for intramuscular injection and this method of treatment was employed in 25 cases treated by Lloyd and Erskine. The ampoules contained a 20 per cent suspension of the compound in 2.5 cc. of olive oil—i. e., 0.5 Gm. in 2.5 cc. Of this, 2.0 cc. was used for each injection given deep into the buttock. The 1 definite objection to using the drug in this manner was the fact that it was painful, in some patients extremely so,

and the pain in some cases persisted for several days.

Toxicity—The clinical reports thus far indicate that the toxic manifestations of the M & B 693 are certainly not encountered with any greater frequency than with the use of sulfanilamide. Most reports indicate that the toxic reactions, when they are manifested, are inclined to be relatively mild. Slight cyanosis and occasional vomiting are the most frequent toxic symptoms encountered.

In the 8 cases of lobar pneumonia treated by Dyke and Reid the drug was well tolerated in most cases. Only 1 case showed any cyanosis and that was very slight. None of the hospital patients had any difficulty in taking or retaining the tablets.

Lloyd and Erskine report in their series of 108 cases, 6 patients developed rashes between the eighth and fourteenth day of treatment. A morbilliform type of drug rash has been the most frequent eruption seen and occurred about the eighth day. Gastrointestinal symptoms amounting to anorexia, nausea, vomiting and abdominal pain occurred in 9 cases. Headache, dizziness, fainting or depression were present in 10 cases. One case of cyanosis was observed, but in 107 blood examinations no abnormal spectra were detected.

The authors conclude that the superior results which they obtained with M & B 693 in amounts which were smaller than were necessary with sulfanilamide certainly lessen the risk of toxic phenomena but in comparable total dosage the 2 compounds appear to be of comparable toxicity.

SULFAPYRIDINE (M & B 693)

At the present time extensive clinical investigation and experimental observations are being carried out in this coun-

try in an effort to properly evaluate this new drug. The Council on Pharmacy and Chemistry of the American Medical Association⁴⁵ have adopted the term "Sulfapyridine" as a nonproprietary name for the drug 2 (Para Aminobenzene Sulfamido) Pyridine.

H. F. Flippin, J. S. Lockwood, D. Sergeant Pepper and L. Schwartz⁴⁹ report a definite reduction in mortality following the use of sulfapyridine in the treatment of 100 cases of pneumococcic pneumonia, seen in several Philadelphia hospitals. In the entire series there were 4 deaths, 3 of which were in type III infections. There were 8 cases of bacteremia with 1 death. The ability of the drug to bring about, within 24 to 48 hours, a critical fall in the temperature followed by prompt clinical improvement was the most significant effect observed from therapy.

The authors conclude that sulfapyridine in their hands was an effective drug in the treatment of typed pneumococcic pneumonia. Also if the toxic possibilities of sulfapyridine are kept in mind and if the patients being treated with the drug are carefully observed, and studied, it is a therapeutic agent with a satisfactory margin of safety.

In a preliminary statement on the status of sulfapyridine P. H. Long⁵⁰ was unable to note specific changes in the capsules of pneumococci observed in peritoneal exudates obtained from mice in which sulfapyridine had been used in the treatment of experimental pneumococcic peritonitis. The experience of the author at this time with the clinical use of sulfapyridine in the treatment of lobar pneumonia has been limited, but in certain instances he feels that the course of the disease has been benefited by the use of the drug. However, the opinion is expressed, that until there is evidence that sulfapyridine is as valuable as spe-

cific antipneumococcus horse or rabbit serum in the treatment of lobar pneumonia, the use of potent types I to VIII and type XIV serum should not be abandoned.

H. L. Barnett, A. F. Hartmann, A. M. Perley and M. A. Ruhoff⁵¹ used the drug in the treatment of 60 cases of pneumonia occurring in infants and children. The beneficial results were similar to those experienced in the treatment of adults, and the authors recommend its early use in suspected pneumococcic infections. Cyanosis due to accumulation of methemoglobin was encountered in most of the cases receiving large doses of the drug, and was readily controlled by the use of methylene blue.

A communication received by The Journal from J. G. M. Bullowa, N. Plummer, and M. Finland⁵² expresses a somewhat less optimistic view concerning the value of sulfapyridine based on present evidence. The authors point out the difficulty of assessing the value of any therapeutic agent in a disease presenting as many complexities as pneumonia, before a large number of properly studied cases have been accumulated. Therefore the authors believe that in regard to pneumonia, sulfapyridine must still be considered as an experimental drug and, as such, should be used only under controlled conditions.

THIOCYANATE

Therapeutics—E. Massie, B. Ethridge and J. P. O'Hare⁵³ reported on the use of sodium thiocyanate in the treatment of 14 patients suffering from uncomplicated vascular hypertension. A lowering of blood pressure was obtained in every case. The average fall ranged from 66 to 21 mm. systolic and 33 to 8 mm. diastolic. In 12 patients marked

symptomatic relief was experienced while receiving thiocyanate, and all felt "good" or "fine." The symptom most affected by the drug was headache or a sense of cephalic fullness. Vertigo and nervousness were diminished and most of the patients experienced a striking sedative effect from the treatment.

Toxic symptoms from the drug were manifested by occasional episodes of transient weakness, and by infrequent attacks of mild epigastric distress. In 1 patient nausea, vomiting and marked weakness occurred, while another patient experienced 3 attacks of angina pectoris.

Dosage and Administration—The dosage of sodium thiocyanate used was *controlled by the blood cyanate concentration*, the optimum level of which was found to range between 5 and 7 mg per cent. The individual dose required to produce and maintain this level varied for different patients.

In the dilution of sodium thiocyanate used, 4 cc contained 0.2 Gm of the active drug. One plan used in starting treatment was to give 0.8 Gm for the first 2 days, and 0.6, 0.4 and 0.2 Gm on consecutive days thereafter. A second method was to give 0.6 Gm for the first 4 or 5 days and then reduce the amount to 0.4 and 0.2 Gm daily. The average maintenance dose usually ranged from 0.2 to 0.4 Gm daily, the maintenance dose being determined in each case according to the level of the blood cyanate found.

The authors conclude that thiocyanate therapy constitutes a useful remedy for the treatment of uncomplicated vascular hypertension. However, the care in selecting patients plus the close observation and regulation of patients while under treatment hardly make this method suitable for handling hypertensive cases by the average physician in the office.

UREA

Therapeutics—P. S. Mertins, Jr.,⁵⁴ has found that urea is of great benefit in the eradication of infections involving the ear. The drug is particularly efficacious in chronically infected middle ears with large perforations in the drum allowing the drug to come in contact with the diseased area. In these cases treatment was carried out by dropping a saturated solution of urea in the ear twice daily. The author states the odor was rapidly eradicated, and all the ears were dry at the time of writing. Patients who underwent radical mastoidectomy were also treated with urea, with equally good results. The treatment almost eliminated the necessity of daily packing, punching and scraping. In patients requiring cleaning of radical mastoidectomy cavities it was found that after approximately 1 week's use of a solution of urea almost all debris was cleaned out, leaving the skin pink and healthy. Mertins has never found that urea harms the delicate epithelium of a radical mastoidectomy cavity, and he has used it on exposed dura without signs of irritation or toxicity. Occasionally on acutely inflamed or raw tissue there is some pain, but this is seldom comparable with that produced by alcoholic solutions. The author's experience has been with the use of urea alone, although he sees no reason why it should not be combined with any form of therapy which the physician might consider applicable in a given case.

Application—The solution is applied with a dropper twice daily, beginning with small amounts, and increasing rapidly if there is no pain. The crystals may be applied directly or with a powder blower. Care must be taken, however, to avoid any caking in the canal or in the powder blower. A small amount

of water or saline solution will usually correct this. The author hopes that this form of therapy will not be looked on as a cure-all, and all other pathologic processes which might be responsible for prolonging infection in an individual searched for and corrected, for the results of urea therapy are due simply to a more adequate removal of the gross and microscopic debris in the recesses of the middle ear, giving nature a fair chance.

G. E. Baker⁵⁵ also reports very satisfactory results during the past year with 25 to 30 per cent solutions of urea for the treatment of wound infections. The author found it stable in solution, non-toxic, and remarkably effective in the removal of wound exudates. The material has also been used in the same concentration for the irrigation of wound sinuses.

VITAMINS

Rapid progress in knowledge continues to be made in connection with the relation of vitamins to human health and disease, and each year seems to bring with it the announcement of at least 1 new essential food constituent. In attempting to summarize the vast amount of experimental investigation and clinical study carried on during the past year the required brevity of this article prevents mention of many papers and excludes critical discussions.

Vitamin A

S. J. Cowell⁵⁶ states that evidence has lately been produced to show that certain fish oils contain a substance resembling, but not identical with, vitamin A, for which the name vitamin A₂ has been proposed. This substance appears to have similar biological effects in experimental animals to those possessed by

vitamin A, and it will remain for future work to decide if vitamin A₂ has precisely the same value in the human body as old vitamin A. Also, recent work has shown that certain well-defined parts of the intestine of certain fish, such as the halibut, yield a considerable greater concentration of vitamin A than the liver oils. As much as one-third of the total weight of such an intestinal oil has been found to consist of pure vitamin A. The discovery of this new source of supply of vitamin A may be a means of providing a clue to some of the functions of vitamin A in human beings.

The most promising clues concerning the function of vitamin A in the human body are the facts that it is concerned with maintaining the integrity of epithelial and nervous tissue and that it enters into chemical combination with a protein to form visual purple. The relation of vitamin A to the formation of visual purple form the basis for the widely used tests for slight degrees of deficiency of vitamin A in human beings, in which the ability to distinguish faintly illuminated objects in a darkened room is measured. Recent reports indicate that the vision of motorcar drivers is improved for night driving as a result of their having received a course of vitamin A concentrate for a week or two. The failure of a baby to respond to a dim light flashed in its eyes by reflex movement of the legs demonstrates very clearly how rapidly an infant may lose its store of vitamin A.

Vitamin A Requirements—The approximate daily requirements for vitamin A are given by L. E. Booher⁵⁷ as 20 to 30 U. S. P. units of vitamin A per Kg. of body weight, or a total of 1400 to 2000 units daily for an adult weighing 70 Kg. appears to be just sufficient for the prevention of night blindness.

Three thousand units of vitamin A daily is suggested as an average require-

ment for the normal adult. Food capable of supplying a large proportion of this vitamin A allowance are milk, butter, eggs and green leafy vegetables.

To provide for growth and development, and a moderate storage of vitamin A in the body, growing children require approximately 6000 to 8000 units of vitamin A daily. In addition to liberal quantities of the above-mentioned foods a small supplement of some fish liver oil is usually sufficient to take care of the needs of the average child.

For pregnant and nursing women 5000 units or more of vitamin A is the recommended daily allowance.

Vitamin B Complex

As a result of the confusion that has arisen in the past because of different terms having been applied to newly discovered factors of the vitamin B complex, E. M. Nelson⁵⁸ designates and describes the members of the B complex as follows:

Vitamin B₁, the antiberiberi vitamin that prevents beriberi in man and polyneuritis in animals.

Riboflavin, a compound necessary for growth in chicks and rats and for the prevention of cataract in rats. It is a component of an oxidation-reduction system of living cells.

P-P factor, a nutritional factor effective in the prevention of human pellagra.

Filtrate factor, a factor for the prevention of a nutritional dermatosis in chicks. Concentrates which contain this factor have been shown to be effective in the treatment of human pellagra and blacktongue in dogs.

Vitamin B₃, a factor necessary for rapid gains in weight and normal nutrition of pigeons.

Vitamin B₄, a factor for the prevention of a specific paralysis in rats and chicks.

Vitamin B₅, a factor necessary for maintenance of weight in pigeons.

Vitamin B₆, or vitamin H, a factor for the prevention of a nutritional dermatosis in rats.

Factor H', a factor necessary for growth of rats.

Vitamin B₁ Sources—The food sources of vitamin B₁ are discussed by H. E. Munsell,⁵⁹ and the results of study show that the vitamin is present in a wide variety of foods. However, in contrast to experience with vitamins A and C, there are few foods of plant or animal origin that may be considered potent sources of the vitamin B₁ factor. Therefore, it is necessary to depend on several food items to furnish the day's supply of vitamin B₁.

Vegetables, including potatoes, form one of the more important groups to be depended on as a source of B₁. Fruits, although only fair sources of the vitamin, nevertheless, are frequently eaten raw, and in large quantities if at all.

Vitamin B₁ tends to be concentrated in the germ portion and outer bran layer of seeds. Legumes, nuts and whole grains are among the good food sources. Refined cereals and flours contain very little of the vitamin because of loss during the refining process.

Eggs, muscle meats and especially the organ meats are rated as good sources.

The article also describes the effect which various processes such as heat, acidity and alkalinity, boiling, canning, storage and freezing may have on the actual loss of vitamin B₁, and points out the fact that it is not the inclusion of a food item in the diet that is important but its actual nutritive value when consumed.

Therapeutics—A summary of the allowable claims for vitamin B₁ are tabulated by M. Fishbein,⁶⁰ taken from the article on vitamins which appears in "New and Nonofficial Remedies" (1938).

In the light of our present knowledge,

1 Vitamin B₁ is of value in correcting and preventing beriberi.

2 Vitamin B₁ may be cited as of value in correcting and preventing anorexia of dietary

origin in certain cases, when the condition to be treated is due to a deficiency of that vitamin.

3 Vitamin B₁ is of value in securing optimal growth of infants and children.

4. Because vitamin B₁ is a dietary essential its administration in concentrated form is of value in some conditions in which difficulty in utilizing ordinary foods in the usual way is encountered.

5 From the summary of various reports on vitamin B₁ requirements it appears that the daily requirement of vitamin B₁ be not less than 50 international units for an infant and 200 international units for an adult.

6. The literature contains experimental evidence suggesting many more functions of vitamin B₁, *e g*, an influence on intestinal motility and neuritis of various types, and also indications of greatly augmented requirements when metabolism is increased as in hyperthyroidism, neuritis of various types, or infections. However, in the light of our present knowledge it seems too early to draw any definite conclusions concerning any specific properties concerning the vitamin in these conditions.

Vitamin C

Studies concerning the therapeutic value of vitamin C in health and disease continue to be subjects of a vast amount of clinical and laboratory investigation. A point of considerable importance which is not yet settled is the significance which ought to be attached to states of "saturation" and "unsaturation" with respect to vitamin C.

Human Requirements of Vitamin C—S. L. Smith,⁶¹ in a discussion of human requirements of vitamin C, mentions 3 levels of requirements to be considered in terms of the minimum quantities of ascorbic acid required: (a) To prevent the slightest decrease in capillary resistance or to maintain uniform excretion of the vitamin barely above that on a vitamin C-free diet, (b) to maintain uniform excretion after a depletion period following a preliminary saturation period, and (c) to maintain the tissues in a state of saturation as determined by various modifications of the test dose

method. The levels of requirement are termed by the author as physiologically indispensable, adequate, and saturation values, respectively.

The estimated requirements for various age groups lie within the following limits of absolute values: Infants, 8 mg. (newly born) to 50 mg. daily; children, from 22 to 100 mg. or more; adults, from 28 to 100 mg. or more.

Claims are constantly being made by physicians that patients suffering from various diseases or surgical conditions respond better to the usual therapy when they are "saturated" with vitamin C.

Therapeutics Vitamin C—“New and Nonofficial Remedies” (1938) allows no definite claims for the therapeutic value of vitamin C other than its relation to scurvy, until further clinical or experimental evidence has substantiated its usefulness in other states. Vitamin C is indicated for the correction and prevention of scurvy, and convincing clinical evidence exists to substantiate its therapeutic value in early or latent scurvy. However, the diagnosis of latent or early scurvy rests on the basis of roentgenologic evidences in the long bones and possibly failure to excrete an optimum amount of cevitamic acid in the urine.

Dental caries, pyorrhea, gum infections, anorexia, anemia, and undernutrition are not in themselves positive indication of vitamin C deficiency. Therefore, the therapeutic value of vitamin C in these symptomatic conditions can only be acceptable when it is definitely known that they are the consequences of a deficiency or suboptimal amount of vitamin C or when there is a pathologic interference with assimilation of the vitamin.

Vitamin D

Existing Forms—Vitamin D, the antirachitic vitamin, has of recent years

been shown to exist in several different forms. C. E. Bills⁶² recognizes at least 10 different sterol derivatives that exhibit properties of vitamin D. Five of these appear to be well understood chemically and 5 are distinguished by fragmentary chemical and physiologic differences. In medicine 2 forms of vitamin D are of prime importance; namely, activated ergosterol and activated 7-dehydro-cholesterol.

Within the past few years the method of expressing vitamin D potency has become standardized. Vitamin D content of preparations intended for use by the physician is determined at present by biologic assay, there being no physical or chemical methods available.

Sources—E. M. Nelson,⁶³ in discussing sources of vitamin D, states that most foods appear to be devoid of demonstrable quantities of vitamin D. Fish which contain much body oil, such as salmon, sardines and herring, are the richest natural sources; eggs are next in importance, and milk fat and meat products contain some vitamin D. Vitamin D milk is now being used extensively as a dependable dietary source of vitamin D.

The individual requirements of vitamin D varies in accordance with the ability of the individual to utilize the calcium and phosphorus of the diet.

Provided a person is ingesting an adequate amount of calcium and phosphorus, vitamin D tends to increase the retention of the minerals in individuals whose retention is poor without vitamin D. Vitamin D ordinarily does not increase the retention of those who have high retention without it.

Infants in general have poor retention and only a very few retain an ample amount of calcium and phosphorus without vitamin D, but at all age periods some persons are found who are not ef-

ficient. The standard vitamin D requirement, therefore, should be the amount which will be satisfactory for those who are least efficient in retaining calcium and phosphorus.

Requirements of Vitamin D—P. C. Jeans and G. Stearns⁶⁴ give as the approximate vitamin D requirement of the full term artificially fed baby as between 300 and 400 units. Breast-fed babies require less vitamin D than babies fed on cow's milk, but for all practical purposes the same amount may be given the breast-fed infants.

For children between infancy and adolescence a daily allowance of at least 750 cc. of milk plus from 300 to 400 units of vitamin D usually insures ample retention of calcium and phosphorus.

For adults the optimal amount of vitamin D, if a need exists, has not been definitely determined. During lactation, however, a daily dose of 800 units is suggested, together with an abundant intake of calcium and phosphorus.

Therapeutics—Vitamin D is recognized as a specific in the prevention and treatment of infantile rickets, spasmodophilia and osteomalacia, diseases which are manifestations of abnormal calcium and phosphorous metabolism. During acute infections, especially of the gastrointestinal tract, vitamin D may prove ineffective because of poor absorption.

E. A. Park⁶⁵ states that 1200 units (12 Gm., or 3 teaspoonfuls) daily of cod-liver oil is sufficient to bring advanced rickets under control within 3 weeks in the majority of cases. Some cases, however, especially premature infants, may require 10,000 to 20,000 units or more to terminate the condition. In these cases it is better to use the non-refractory type of rickets, may require concentrated forms of vitamin D. Some older children, especially those having a

doses of vitamin D as high as 60,000 units or more daily to cure the condition.

There appears to be clinical evidence to justify the statement that vitamin D plays an important rôle in tooth formation and maintenance of normal tooth structure, but there is no proof to justify the claim that adequate vitamin D intake will prevent dental caries.

Vitamin K

Distribution — A. E. Osterberg⁶⁶ gives credit to Dam and his coworkers in Copenhagen for first suggesting that a deficiency of an accessory dietary factor is concerned in the experimental production of generalized hemorrhage of certain animals. This dietary factor has been designated as vitamin K, and has been demonstrated to have a fairly wide distribution in nature. Dam's experimental work showed that the substance was of a fat soluble type and that hog liver oil, cabbage, spinach, tomatoes and alfalfa were effective in supplying this deficiency. However, cod-liver oil, wheat germ oil, carotin, cevitamic acid, egg albumin and ultraviolet irradiation were ineffective. Of the grains used, alfalfa proved to be the best source of the vitamin.

In attempting to obtain sufficient material for clinical trial at the Mayo Clinic, preparation of vitamin K obtained from fish meal was used because the involved procedure for concentration of the K factor from alfalfa made this source unsatisfactory. This source of vitamin K had previously been suggested by Almquist in California. It was demonstrated by the author that such fish meal, when allowed to putrefy, was a good source of vitamin K which could be extracted later by means of petroleum ether. Following the removal of the solvent, an oily residue remained which proved to have a high protective power for hemor-

rhagic chicks, and to be protective for patients who have jaundice, a prolonged prothrombin time and a tendency to hemorrhage.

Chemical Nature—The author states that little is known of the chemical nature of vitamin K, and what meager knowledge we do have came from Almquist and his coworkers. The material is nonnitrogenous and it contains an aromatic nucleus. No phosphorus or sulfur is present. It is not particularly stable to the general chemical procedures and apparently does not contain a sterol ring. It is alkali labile and fairly heat stable. It has an apparent molecular weight of about 600 according to the author.

Methods of Assay—The author cites the method used by Dam, the so-called curative method. Blood samples are taken from chicks which have been on a diet deficient in vitamin K for at least 3 weeks and are assumed to be depleted in vitamin K. The plasma is diluted with Ringer's solution and is caused to coagulate by the addition of a sufficient amount of a clotting agent to make the clotting time normal. The unknown substance to be assayed is mixed with the deficient diet, fed to the chicks and the blood samples are retested for clotting time after several days. From this data the dietary level of the K factor is determined.

Therapeutics—H. R. Butt, A. M. Snell and A. E. Osterberg⁶⁷ report on the use of vitamin K and human bile or animal bile salts in 18 patients who had obstructive jaundice. According to the authors, complete biliary obstruction and liver damage were present in most of the 18 cases. Several cases did not show any considerable elevation in prothrombin time but vitamin K and bile salt were given as a prophylactic measure.

From the results of the clinical studies carried out by the authors, certain facts seem fairly well established in relation to the clinical use of vitamin K. Their conclusions were that the administration of vitamin K together with bile or bile salts to patients who have jaundice has reduced elevated prothrombin times to within normal limits and in certain cases probably prevented hemorrhage or has inhibited actual hemorrhage. Bile alone given to a patient receiving an adequate diet has resulted in shortening of the elevated prothrombin time. In 1 individual the administration of vitamin K alone, where bile was absent from the intestinal tract, had little or no effect in decreasing the elevated prothrombin time. Finally, the authors believe that while considerable experimental work and clinical experience is needed to establish a routine for the use of vitamin K and bile salts in the preoperative and postoperative jaundiced patient with a hemorrhagic diathesis, nevertheless, the results so far have been very encouraging.

Vitamin Oils

Therapeutics—The therapeutic effect of ointments containing varying amounts of vitamin A and vitamin D on controlled burns produced on pigs and rabbits was studied and reported on by C. B. Puestow, H. G. Poncher and H. Hammatt.⁶⁸

The time and character of local wound healing was determined and compared with untreated controls and burns treated with tannic acid. Burns treated with 5 per cent tannic acid solution healed in the same length of time as untreated controls of similar average size. The application of vitamin-free olive oil ointment to slightly larger burns was followed by complete healing in the same length of time as the controls. Cod-liver oil ointment shortened the period of heal-

ing by 25 per cent Burns which averaged 50 per cent larger than the controls were treated with 3 high-vitamin ointments containing no vitamin A but high in vitamin D, having a low vitamin A to vitamin D ratio, and having a high vitamin A to vitamin D ratio. The time of healing was approximately 25 per cent shorter than in the smaller control lesions and those treated with tannic acid. The response to the various high-vitamin ointments employed was approximately the same. Histologic studies of the scars of all healed burns revealed no characteristic difference for the various therapeutic agents employed.

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